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CONGENITAL MULTICYSTIC DYSPLASIA OF THE KIDNEY

REPORT OF NINETEEN CASES WITH DISCUSSION ON THE ETIOLOGY. NOMENCLATURE AND CLASSIFICATION OF THE CYSTIC DYSPLASIAS OF THE KIDNEY

BY

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Congenital multicystic dysplasia of the kidney
»Multilocular cystic kidney»
Solitary renal cysts
Congenital polycystic disease

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Introduction

During recent years reports have accumulated on the unilateral multicystic kidney (Ravitch & Sanford 1949, Spence 1955, Hooper 1958). Most of the reports have been based on only single or very few cases. The most recent review only comprises some thirty cases (Coppridge & Ratliff 1958). Recently, mentions have been found in the literature suggesting greater frequency of this kind of cystic disorder (Grob 1957, Lipton & Scordamaglia 1957, Longino & Martin 1958, Hooper). On the other hand, apparently similar lesions have been reported under various headings (Trillat, Guilleminet & Boulez 1957, Abeshouse 1956, Hennig 1954, Kempf 1956, Herczec, Rutkai & Deák 1956), especially under multilocular cystic kidney (Lauret 1956, Powell, Shackman & Johnson 1951). Hence, great confusion seems to exist on the nature of the lesion.

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Material

Our material consists of 19 cases of multicystic dysplasia of the kidney found at the Pediatric Department of the University Central Hospital during the years 1947—1958. The ages of our patients varied from 1 hour to 1 year 8 months. The diagnosis was verified operatively in 6 cases, in 2 of which a later autopsy was performed. In the others the diagnosis was not made until at autopsy. In all but 2 of the autopsied cases, microscopic examination of the diseased organ was made. As far as we know, such a large material has not been reported previously. Further, »data assembled by postmortem studies in infants and children are of far greater accuracy and statistical value than in adults. In adults it is rarely possible to be certain if the lesion was acquired or congenital» (Campbell 1954). We therefore consider the report of the cases justified. Further, we should like to discuss the etiology, the suggested name and definition of congenital multicystic dysplasia of the kidney, and suggest our basis of classification of congenital cystic kidney dysplasias.

Preliminary Definition

By congenital multicystic dysplasia of the kidney we mean a macroscopically cystic deformity of the kidney similar to that described *e.g.* by Schwartz 1936, Ravitch & Sanford, Spence and Spence, Baird & Ware 1957. The deformed kidney is composed of cysts varying in size and number, which give to the organ the appearance of a bunch of grapes. The cysts are held together by connective tissue. Macroscopically very little, if any, normal renal parenchyma is seen. The disorder is said to be unilateral, but bilateral cases have been reported (Longino & Martin, Hooper). Microscopically islands of normal renal parenchyma may be visible, but as a rule, these are minute. The stroma between the cysts is composed mainly of primitive connective tissue, in which various dysplastic structures are embedded (Williams 1958). Bilateral multicystic kidneys have a similar microscopic structure to unilateral ones (Hooper).

ney was available. There was congestion and hemorrhages in the left, contralateral kidney but otherwise the structure was normal.

Case 4. O.A., a boy (No. 3842/52) who was sent to hospital when newborn for cyanosis and difficulty in swallowing. There was a systolic murmur in the heart, heard parasternally on the left. The plain abdominal roentgenograms were normal. Thorax X-ray: Th I was a semi-vertebra, the heart pathologically dilated and its apex considerably elevated from the diaphragm. Films with contrast meal revealed an atretic esophagus. The patient died in a couple of hours with pronounced cyanotic symptoms.

Autopsy showed transposition of the aorta and the pulmonary artery and an infundibular and valvular pulmonary stenosis. There was an extensive defect in the interventricular wall. The right ventricle was hypertrophic. The esophagus was atretic and ended in a cul-de-sac above the bifurcation. There was a fistula from the right main bronchus to the lower segment. The left kidney was normal, the right one was situated on the margin of the minor pelvis and reminded a bunch of grapes formed by cysts. Grossly, no renal tissue was observed. The genitals were normal.

Microscopic examination of the kidneys: The samples showed a few normally organised areas of renal tissue in which the proximal tubuli were large and cystic with cuboidally flattened epithelium. The structure of the glomeruli was otherwise normal for the age except that Bowman's capsules were cystic in many places. A part of the glomeruli had been destroyed and gave a hyalinised appearance. A large cystic portion was attached to this tissue clearly recognisable as kidney. The cysts were lined with endothelium-like or shallow cuboid epithelium. Their walls consisted of connective tissue with muscular strands dispersed throughout it. The connective tissue was generally dense but in places undifferentiated and primitive and enveloping the primitive tubuli concentrically. The epithelium of these tubuli was ciliated and cylindrical. There were rudimentary glomeruli in the walls of the large cysts. No connection was established by nephron dissection between these glomeruli and the cysts; the nephrons ended in a cul-de-sac. No urothelium proper was visible. There was also testicular tissue with infantile seminiferous tubuli in the area of the sample. The left kidney was normal microscopically.

Case 5. V.A., a girl (No. 3923/53), was the fourth child of the family. She was sent to hospital at the age of 1 month for tumour palpated on the left side of the abdomen. Her general condition had been good and she was asymptomatic. A fist-sized tumour was palpable in the left upper quadrant of the abdomen. Urine withdrawn by catheter showed some leucocytes and numerous Gram-negative rods; non-protein nitrogen was normal. Plain roentgenograms of the abdomen revealed on the left an extensive tumour which filled the left half of the abdominal cavity and pushed the bowels towards the median line. Excretory urography revealed excretion from the right kidney only.

Extirpation of the tumour was performed when the patient was 5 weeks old. The multicystic tumour located retroperitoneally on the left was eradicated; the renal blood vessels and ureter passed it anteriorly. The latter was cut from below. Postoperatively recovery was uneventful. Her condition 4½ years after operation was still good.

Microscopic examination of the tumour: Normally organised renal tissue was seen between the large cysts. The glomeruli were of fetal type. Bowman's capsules were covered with cuboidal epithelium. The glomeruli were avascular, some of them were hyalinised. The proximal tubuli were dilated and their epithelium shallow, cuboid. They showed colloid structures. Several large cystic cavities were covered with urothelium. The wall consisted of connective tissue which displayed dispersed smooth muscular fibres. One larger cyst was lined with a single-layered flat epithelium. In the intercystic

Case Reports

Case 1. S.R., a boy (No. 1892/47) of 7 months, who was taken to hospital for treatment of his diarrhea. His general condition was poor, stools were loose, mucous and bloodstained. He vomited blood. The pharynx was inflamed. The testicles were in the scrotum. The child died immediately after admission.

At *autopsy*, gastroenteritis was established as the cause of death and a cloudy swelling was found in the liver. The finding was otherwise normal apart from the absence of the left kidney and the presence at its site of 2 cysts the size of the tip of a little finger from between which the ureter issued. There was no mention of the blood vessels of the hilus. *Microscopic examination* of the left kidney: The cysts were lined with cuboidal epithelium. The walls consisted of connective tissue containing smooth muscular fibres. The interjacent connective tissue showed primitive tubuli surrounded by immature cellular tissue resembling the stroma of Wilm's tumour. Approximately ten smaller cysts in the samples were coated with an epithelium of proximal tubules. The walls of these cysts too presented muscular fibres in delicate connective tissue stroma. There was no normally organised renal tissue in the slides. The walls of the large cysts revealed rudimentary glomeruli, the Bowman's capsules were lined with cuboidal epithelium. The stroma contained numerous thick-walled arteries with hyalinised walls and a rich capillary network. The stroma showed lymph follicles. There was no cartilage. The right kidney was normal microscopically.

Case 2. R.R., a girl (No. 2599/49) who was the third child of a mother of 35. She was admitted at the age of 9 days for esophageal atresia. On entering the hospital she was in poor general condition, suffering from respiratory difficulties. The catheter passed 11 cm into the esophagus. The abdomen was distended and large. Non-protein nitrogen was 97 mg%. The child died c. 6 hours after gastrostomy.

Esophageal atresia was established at *autopsy*. There was a blind upper esophageal segment and a fistula from the lower segment to the bifurcation. Both lungs showed massive pneumonia. The right-side kidney was normal in structure, weight 14 g. The left kidney was multicystic and resembled a bunch of grapes. *Microscopic examination*, performed on the right kidney only, demonstrated pyelonephritis. There was no dysplastic tissue. No specimen was available from the left kidney.

Case 3. K.M.L., a newborn girl (No. 95/51). Second child of a mother of 28, she was born in a state of deep suspended animation. The first child was a healthy girl of 5. The child was sent to hospital with the diagnosis fetal erythroblastosis in very poor condition. She died in the outpatient department.

Autopsy revealed atelectatic lungs and microscopy revealed abundant hyaline membranes in the alveoli and bronchioli. There were numerous ecchymoses on the serous membranes. The left kidney and the bladder were normal in structure. The right kidney as a whole was a multicystic formation of $5 \times 5 \times 7$ cm. The ureter leading from it showed a lumen at least in places in the initial part; near the bladder the ureter tapered into a threadlike shape and became fully atretic. The genitals were normal. No microscopic specimen of the cystic kid-

places primitive tubuli surrounded by immature connective tissue. The epithelium of these tubuli was ciliated. In two places there were wider cysts, also surrounded by immature connective tissue. The epithelium of these cysts was cuboidal in form. No cartilage was found in the sample. Lymphatic tissue occurred in islets. The ureter wall consisted of muscular and connective tissue fibres. The ureter had no lumen.

Case 8. K. J., a boy (No. 2183/56). The first child of his parents. He was born at term. He was taken to hospital at the age of 1 week for tumour diagnosed on the right side of the abdomen which was distended, particularly on the right. The spleen was palpable and slightly enlarged; the left kidney was normal to palpation. An approximately apple-sized, uneven tumour was felt on the right between the costal arch and the iliac crest. The testicles were in the scrotum. The urine analysis was normal. Blood urea nitrogen was 11 mg per cent.

Excretory urography established poor excretion on the left side. Some contrast medium entered the bladder. There was no excretion from the right side. Yellowish fluid resembling urine was obtained by puncture from the right kidney.

On *operation*, at the age of 18 days, grape-like tumour was removed from the right kidney area. It measured 6 × 4 × 4 cm and consisted of 6 cysts 1—6 cm in diameter. There was normal renal tissue between the cysts. One cavity, 1 cm in diameter, obviously represented the renal pelvis but the opening of the ureter seemed to be blocked. There was no intercommunication between the cysts. The blood vessels of the hilus were of normal appearance. — Postoperatively the child died of septicemia due to impaired healing and infection of the wound.

Microscopic examination showed normally organised renal tissue in islets in the connective tissue between the cysts. The structure of the glomeruli was normal for the age. Some of the proximal tubuli were dilated and their epithelium was cuboidal. There were colloid structures in places. Normal-looking tubuli lined with a higher epithelium were also seen. In the parts corresponding to the medulla the structure of the tubuli accorded with that of collecting tubuli. The epithelial lining of the cysts varied in height. The cyst walls consisted of connective tissue, intermingled with smooth muscular fibres. The tissue between the cysts was composed of connective tissue of varying density with numerous blood-filled capillaries and thick-walled larger vessels. In addition atypical glomeruli with cystic Bowman's capsules were seen. The cartilaginous islets were enveloped in undifferentiated connective tissue. Similar connective tissue also surrounded the primitive tubuli which occurred dispersed in the interstitial tissue. One sample displayed a cyst lined with transitional epithelium. The cyst corresponded to the renal pelvis in structure. The interstitial tissue revealed numerous thick-walled blood vessels and a rich capillary network.

The left kidney was normal on both gross and microscopic examination.

Case 9. K. R., a girl (No. 3366/56) was the third child, premature, of a mother of 21. The other children were healthy. Birth weight 980 g. The child was taken to hospital because of her prematurity. The cholesterol Wasserman reaction and Kahn's test from the mother's blood were positive, the other tests negative. The child died from the sequels of infection one month after birth.

Autopsy showed congenital syphilitic cirrhosis of the liver which together with bilateral pneumonia and immaturity must be regarded as the cause of death. The left kidney which weighed 7 g had a normal appearance; the right kidney was replaced by a cystic multilocular mass.

Microscopic examination: The cyst walls consisted of connective tissue and smooth muscle. The epithelium lining the cysts varied in height from cuboidal to flat endothelial-like. The cyst in connection with the ureter was lined with urothelium. The cysts were separated from one another

tissue islets with collecting tubuli were seen which though wide and cystic were fairly normal in appearance. There were also islets of primitive tubuli covered with ciliated cylindrical epithelium. They were surrounded concentrically by primitive connective tissue. The intercystic tissue also showed hyaline cartilaginous islets surrounded by the above-mentioned connective tissue and, more distantly, by collagenous connective tissue. The arteries were almost blocked, displayed proliferation of the media.

Case 6. E., a girl (No. 2532/53). First child of a mother of 19, she was delivered 1 month prematurely. She was born in a state of deep suspended animation. No external deformities were observed. Died at the age of 1 hour.

At *autopsy* the child was found to be a well-developed premature. The immediate cause of death was bilateral pulmonary hemorrhage. The right kidney and ureter were absent. The left kidney weighed 5 g. It was a cluster of cysts, $1\frac{1}{2} \times 2 \times 4$ cm, containing clear fluid. The cysts, 7 in number, ranged from $\frac{1}{2}$ to $2\frac{1}{2}$ cm in diameter. No renal tissue was found on gross examination. The ureter led from the renal pelvis enveloped by the cysts, and descended as usual into the bladder. The genitals were normal.

Microscopic examination of the left kidney: There was no normally organised renal tissue in the sample area. The sample showed an extensive cavity lined with transitional epithelium. The epithelium of the numerous minor cysts was single-layered and cuboidal. The walls of these cysts consisted of dense collagenous connective tissue and smooth muscular fibres. The intercystic tissue was loose, rich in blood vessels and showed scattered glomeruli. The structure of these glomeruli was primitive and there were, in close association with them, loops reminiscent of proximal tubuli. Bowman's capsules were cystic. Primitive tubuli appeared in places. Their epithelium displayed stereocilia. There was primitive connective tissue around the tubuli, though not concentrically arranged. No cartilage was seen in the sample. The interstitial tissue revealed numerous thick-walled blood vessels and a dense capillary network. There was some hyalinisation in the blood vessel walls.

Case 7. G. J., a girl (No. 1040/55). The first child of a mother of 28. She was delivered 2 weeks prematurely in a breech presentation. Her birth weight was 2.400 g. The child was flaccid and of cyanotic pallor postnatally; respiration was poor from the outset. Died at the age of $3\frac{1}{2}$ hours.

At *autopsy* the air content of the lungs was found to be reduced. The microscopic samples taken from the lungs showed hyaline membranes in the alveoli and bronchioli. Two clusters, $2 \times 1 \times 1\frac{1}{2}$ cm, of 4 and 5 cysts, respectively, were found bilaterally at the site of the kidneys. The cysts were an average of 1 cm in diameter, non-communicating and contained clear fluid. These formations were associated with the ureters which were thick and rigid. The ureters seemed to be closed. They ended in a bladder the size of the little-finger tip which opened into the cloacal cavity in the lower portion of the vagina. The uterus was bipartite. An ovary was related to both parts which opened separately into the upper portion of the vagina.

Microscopic examination of the kidneys: No normally organised renal tissue was found in the samples taken from the kidneys. The numerous multiform cysts were lined with cuboidal epithelium. The cyst walls consisted of collagenous connective tissue containing smooth muscle fibres. The intercystic tissue consisted of loose connective tissue with numerous blood-filled capillaries and thick-walled blood vessels. The cyst walls revealed atypical glomeruli with a cystic capsule of Bowman. The intercystic tissue displayed scattered groups of tubuli localised in many places in the vicinity of the walls of the cyst cavities. Their epithelium was high-prismatic, cylindrical; no cilia were distinguished. In addition, the intercystic tissue revealed in a couple of

follow-up; he had been well at home in every respect. Catheter urine was normal, blood urea nitrogen 15 mg per cent.

In post-operative urography excretion commenced on the left immediately; the renal pelvis and the calyces were very wide and clumsy. The ureter was normal.

Microscopic examination of the right kidney: The sample showed a small area of normally organised renal tissue where the structure of the glomeruli was normal for the age. The distal tubuli were dilated and their epithelium was cuboidal. There were no colloid structures. Normally organised renal tissue was seen between the large cysts, near the cavity which was lined with urothelium. There were several tubuli, reminiscent structurally of collecting tubuli, in the cavity wall. The walls of the different-sized cysts consisted of connective tissue and smooth muscle, and the cysts were lined with shallow cuboidal epithelium. The tissue between the cysts was loose connective tissue containing blood-filled vessels. It also revealed isolated glomeruli and groups of tubuli. The vascularisation of the glomeruli was poor and some of them were hyalinised. Also primitive tubuli surrounded by concentrically organised embryonal connective tissue were seen. The stroma displayed foci of lymphoid tissue. There was no cartilage.

Case 12. K. L., a girl (No. 3093/57), was the third child of her parents. Birth weight 3.450 g. She was taken to hospital at the age of 2 days for atresia of the esophagus The anus opened into the vaginal vestibule and emitted air and feces.

The patient was operated on at the age of 3 days for esophageal atresia. Scleredema developed postoperatively and the child died at the age of 10 days.

Autopsy showed a neat esophageal anastomosis. The fistula between the esophagus and the trachea was closed. There were three spleens. In addition a vestibular anus was found. There was massive pneumonia bilaterally. The right kidney was normal, weight 20 g; the bladder was normal. The left kidney consisted of 5 transparent cysts. It weighed 2 g and measured 2 × 1½ × 1 cm. The cysts ranged from ½ to 1 cm in diameter. The cysts were not intercommunicating. No renal tissue was seen grossly. The ureter was connected with the cluster in a thread-like form and was blocked throughout its length.

Microscopic examination: The left kidney showed islets of normal renal tissue between the cysts. The glomeruli were vascularised. Bowman's capsules were covered by cuboidal epithelium. In the areas corresponding to the cortex the convoluted tubuli were cystic and the epithelial lining flat. There were colloid structures. The epithelium of the loops of Henle was normal. No collecting tubuli were distinguished with certainty, nor were structures corresponding to the renal pelvis found. The majority of the samples consisted of cysts of different sizes with cuboidal epithelium. The cyst walls consisted of collagenous connective tissue which showed isolated smooth muscle fibres. There were rudimentary glomeruli in the walls. The intercystic tissue of the cysts was loose connective tissue with large thick-walled arteries and numerous angiomatous lesions. The intercystic tissue contained islets of undifferentiated connective tissue with primitive tubuli centrally. There was no cartilage.

Case 13. K. E., a boy (No. 3368/57) who was hospitalised at the age of 5 days for atresia of the esophagus. The patient looked miserable and there was scleredema. His hands had a 90 degree radial flexion and had only four fingers each. The testicles were in the scrotum. The catheter passed 11 cm into the esophagus. Roentgenograms revealed bilateral pneumonia and a good deal of air in the intestines. The radius, 1st metacarpal bone and the thumb were missing on both sides. When the patient was 6 days old the esophageal atresia with tracheo-esophageal fistula was corrected through posterior extrapleural mediastinotomy. He died on the day of the operation at the age of 7 days.

by connective tissue of varying density in the area of which there were sporadic fetal-type glomeruli with poor vascularisation. Bowman's capsules were cystic in some of the glomeruli. There was concentrically organised embryonal connective tissue around the slit-like tubuli. The tubuli were dichotomously dividing, lined with multi-layered, high cylindrical epithelium with polypous protrusions into the lumen. There were some cartilaginous islets, in connective tissue. Small, normally organised islets of renal tissue were seen between the large cysts. The gromeruli were fetal and the capsular spaces cystic in the area of these islets. Some of the glomeruli were rudimentary. No normal convoluted tubuli were found. There were primitive tubuli in the areas corresponding to the medulla. The interstitial tissue revealed numerous angiomatous lesions. — The left kidney was microscopically normal.

Case 10. M., a boy (No. 3544/56). Died when aged 1 hour. The diagnosis was right-sided multicystic renal tumour.

Autopsy showed that the child was a premature. Both hip joints were dislocated. There was anal atresia. The right testis, the urinary bladder, both ureters and the left kidney were missing totally. The right kidney was replaced by a multicystic formation of 5 × 4 × 2½ cm. The tumour weighed 45 g and its cysts contained 30 g of clear yellowish fluid. In the medial part of the cystic cluster a cavity was found the inner surface of which resembled, to the naked eye, the inner surface of the renal pelvis. There was anal atresia with recto-vesical fistula and patent urachus. A short ureter-like stump with a lumen 1 mm in diameter was attached to the site of the fistula. There were 6 cysts in all ranging from ½ to 2 cm in diameter. There was no intercommunication between them.

Microscopic examination of the right kidney: No normally organised renal tissue was seen. The walls of the multilocular cystic formation were composed of undifferentiated connective tissue. The epithelium of the cysts was mostly cuboidal but the height varied in places. The area of immature connective tissue showed some cartilaginous islets and primitive tubuli with high, ciliated epithelium. In the connective tissue between the cavities were scattered atypical glomeruli with cystic Bowman's capsules. Some of these glomeruli were disintegrating, partly hyalinised. There were scattered, mostly normal-sized tubuli also in the interstitial tissue. They sometimes occurred in the vicinity of the glomeruli and their epithelium was low as in the proximal tubuli. Some of the tubuli were dilated. There were also narrow tubuli with relatively high 2-layered epithelium and muscular fibres in the surrounding embryonal tissue. A clearly demarcated area containing testicle tissue was seen in the centre of the cystic group. Its structure was normal for the age. Epididymal tissue was seen associated with it.

Case 11. T. A., a boy (No. 275/57), was the third child of a mother of 29. After birth a right abdominal tumour was found and the boy was taken to hospital. There a soft, smooth-surfaced, mobile tumour, the size of a small egg, was found to the right and slightly inferiorly of the umbilicus. On the left there was a somewhat larger normal-shaped kidney. The testicles were in the scrotum. Catheter urine was normal. Blood urea nitrogen was 6 mg per cent.

Excretory urography showed on the left a markedly hydronephrotic kidney. The ureter was not dilated. Abundant contrast medium accumulated in the bladder. No excretion was found on the right side.

An *operation* was performed at the age of 15 days. At the site corresponding to the kidney a grape-like, cystic tumour was extirpated. The cysts were pale, transparent; a thin ureter led from the hilar region and a thin vascular pedicle entered it. The left kidney was palpated. It was rather long and revealed fetal lobulation. The pelvis was hydronephrotic and fluctuating. The patient had a good post-operative recovery. He visited the hospital a year later for a

connective tissue and smooth muscle. The epithelium varied from cuboidal to flat endothelial type. In one sample was seen a separate area containing tissue which differed completely from its environment: tubular formations which resembled epididymis structurally. — The right kidney was normal microscopically.

Case 15. R. H., a boy (No. 590/58) who was the illegitimate first child of his mother. Progress was poor. The patient came to hospital for cardiac examination at the age of 1 year 8 months. He was a delicate child weighing 9.9 kg, height 80 cm. A continuous murmur was heard on the left in the II and III intercostal region. A fairly soft, mobile tumour, the size of a small egg, was felt at the site of the left kidney. Both testicles were in the scrotum; there was slight phimosis. The urinary specimens were normal. Blood urea nitrogen was normal.

Excretory urography revealed no excretion on the left.

Left-sided *nephrectomy* revealed a multicystic formation in the region of the kidney. The cyst situated most caudally was the largest, 5 cm in diameter. No renal tissue was found. The tumour, 10 × 5 cm, extended caudally to the promontory. The blood vessels of the hilus were normal; they were tied. The ureter appeared normal, was detached distally and cut. The patient made a good recovery. When he was 1 year 11 months old left thoracotomy was performed; the open arterial duct was ligated. The patient recovered well also from this operation.

Microscopic examination of the left kidney: The slides showed small islets of fairly normally organised renal tissue. There were, however, fewer glomeruli and convoluted tubuli than usual in the area of the islets. Some of the convoluted tubuli were atrophic, some markedly dilated and filled with a colloid-like substance. The epithelium of the dilated tubuli was shallow here but cuboidal elsewhere. The glomeruli were lined with cuboidal epithelium. Bowman's capsules were cystic in some places; there were a few primitive tubuli encircling the glomeruli at a site corresponding to the cortex. There was connective tissue of varying density and with wide blood vessels between the islets of renal tissue. Some of them were thick-walled, others again thin-walled veins. There were isolated glomeruli with cystic Bowman's capsules in the connective tissue. A part of the lobuli of these glomeruli was scarred, a part normal, vascular. There were also islets composed of embryonal connective tissue which was fully undifferentiated. Here and there this embryonal connective tissue, concentracally arranged, enveloped the primitive ducts which showed a dichotomous division. The epithelium lining these ducts was pseudostratified and stereociliated. In some places the epithelium projected into the lumen in a polypoid manner. The walls of the large cysts consisted of dense collagenous connective tissue and smooth muscle. The epithelium covering the cysts varied from cuboidal to shallow, flat endothelial. No intercommunication was found between the glomeruli in the cyst wall and the cyst. There were no cartilaginous islets in the samples.

Case 16. L. H. O., a boy (No. 447/58) who was the second child of his parents. The first baby was healthy. There was abundant green amniotic fluid. The child was in a state of suspended animation when born. Roentgenogram taken after birth showed the ventricle to be filled with air but the intestines to be void of air. The patient was hospitalised at the age of 4 days with the diagnosis of intestinal atresia. A mass the size of a small egg was palpable to the right of the umbilicus. On the right was an inguinal hernia. The testicles were not in the scrotum. The urine albumin test was weakly positive. Chest roentgen films showed massive pneumonia, the esophagus, filled with air, ended in a cul-de-sac at the level of the 3rd rib. There was air in the intestines. Extrapleural thoracotomy and repair of the esophagean atresia was per-

Autopsy revealed an operated esophageal atresia. There was massive pneumonia bilaterally. The left kidney and the bladder were normal. The right kidney, measuring $3\frac{1}{2} \times 2 \times 2$ cm, was composed of cysts. The diameter of the cysts, 10 in all, was 0.5—1.5 cm. No renal tissue was observed grossly. There was no intercommunication between the cysts. The ureter was thick-walled and wide both above and below a stenosis in the middle.

Microscopic examination of the kidneys: No normally organised renal tissue was found in the sample from the right kidney. The bulk consisted of cysts. The tissue lying between them, consisted of embryonal undifferentiated connective tissue. The intercystic tissue revealed primitive tubuli with pseudostratified, ciliated epithelium. Besides primitive tubuli there were also primitive glomeruli with cystic Bowman's capsules. The glomeruli were lined with cuboidal epithelium. The walls of the large cysts consisted of loose collagenous connective tissue and smooth muscle. The walls showed atypical glomeruli with incipient hyalinisation. In some preparations tubuli encircling the glomeruli were seen, structurally these tubuli corresponded to the proximal tubuli but were unusually narrow. There were no cartilaginous islets. Lymphatic tissue was scanty. Blood vessel formations were present. The left kidney was normal microscopically.

Case 14. L. T., a boy (No. 1941/57) who was the second child of his parents. The pregnancy was normal. He was sent from a rural hospital for suspected abdominal tumour at the age of 5 months. The general condition was good. The abdomen was distended on both sides, slightly more on the left. A mass the size of about a child's fist was palpable on the left; it did not feel very hard. The albumin test in the catheter urine was positive. The urinary sediment was normal. Blood urea nitrogen was 14 mg per cent.

Excretory urography established normal excretion on the right and the renal pelvis and calices were normal. The ureter was normal down to the bladder. No excretion was observed on the left where there was a dense, roughly fist-sized shadow.

Left-sided *nephrectomy* was performed at the age of 5 months. The tumour was multicystic, the size of 2 fists. The ureter and the renal vessels were running between cysts. Removal was easy by extirpation. The adrenal gland was seen like a flat disk at the upper pole. A supernumerary spleen was found. Grossly, there was a conglomeration, sized $12 \times 8 \times 9$ cm, of c. 12 cysts ranging from 3 to 6 cm in diameter. There was no intercommunication between them. There seemed to be renal parenchyma in the wall of one cyst. The ureter was narrow and closed. — The postoperative course was uneventful.

Microscopic specimens displayed small renal areas organised fairly normally. The glomeruli were infantile, in places hyaline. The outer layer of Bowman's capsule was thick and covered by cuboidal epithelium. Wholly rudimentary glomeruli were also found. The tubuli of the cortex were partly dilated and filled with colloid-like material, partly atrophic. In the middle of normal tissue there were angiomatous blood vessels. Primitive, gaping ducts were found in the area corresponding to the medullary zone. These ducts were enveloped in immature embryonal connective tissue containing smooth muscle fibres. Their epithelium was stratified, cylindrical. Stereocilia were seen in many places. The division of these ducts was dichotomous. The renal areas of normal appearance were separated by connective tissue varying in maturity and density. It contained numerous angiomatous vessels and a few cartilaginous islets. In the area of the connective tissue individual infantile and rudimentary glomeruli were seen which serial section revealed to lack intercommunication with the tubuli and the large cysts. Bowman's capsules were cystic in many places, filled with a colloid-like substance. The area of the stroma showed primitive tubuli surrounded by embryonal connective tissue. The walls of the large cysts consisted of collagenous

connective tissue in the area of which was a capillary network and wide thick-walled blood vessels. The connective tissue showed islets consisting of undifferentiated connective tissue with primitive tubuli centrally. In a few places primitive connective tissue enveloped cartilaginous islets. The large cyst-like cavities were lined with cuboidal single-layered epithelium. The cyst wall consisted of dense collagenous connective tissue in which primitive glomeruli were seen. Their capsules were cystic. — In the samples taken from the right kidney the tubuli were wide and the epithelium lining them shallow. There were small foci of inflammatory cells between the cortical and the medullary zone.

Case 18. N. R., a boy (No. 3993/58) with a birth weight of 2,760 g. The child had vomited and made poor progress. He was admitted to hospital at the age of 1 month, unconscious and vomiting blood. Bilateral pneumonia was established. No masses were palpated in the abdomen. The testicles had descended. There was albuminuria. Blood urea nitrogen was 71 mg per cent. Despite 3 weeks of antibiotic and fluid therapy the patient failed to improve in condition and finally died.

Autopsy revealed a cystic formation, 4 × 5 × 3 cm, at the site of the left kidney. The cysts varied from 1.5 to 3 cm in diameter. No renal tissue was seen grossly. The ureter, in the upper part of which no lumen was seen, was connected with the centre of the cystic formation and terminated in the bladder in the normal way. The right kidney was 6 × 4 × 3 cm. Its lower pole was cystic. There were several recesses in the area of the upper pole. The cortical zone was clearly defined. There were yellowish strands of pus on the border between the cortical and medullary zones and in the part corresponding to the medulla. The renal pelvis was unusually large and its mucosa was blood-filled. The ureter was normal. There were pneumonic areas bilaterally in the lungs. Nothing special was observed in the other organs.

Microscopic examination of the kidneys: The samples taken from the left kidney showed large cysts lined with shallow cuboidal epithelium. The cyst walls consisted of connective tissue with smooth-muscle fibres dispersed throughout it. There were some rudimentary glomeruli in the walls. The tissue between the cysts consisted of connective tissue of varying density. There were numerous thick-walled blood vessels and angiomatous formations in its area. The connective tissue revealed scattered lymph follicles and cartilaginous islets. There were also primitive tubuli lined with ciliated epithelium and concentrically surrounded by embryonal connective tissue. No normally organised renal tissue was found in the samples. No lumen was demonstrated microscopically in the sample taken from the upper part of the ureter.

In the lower pole of the right kidney the microscopic picture resembled that of the left kidney. There were, however, normally organised renal areas between the cysts. The samples taken from the upper pole showed pronounced inflammatory changes on the border between the cortical and medullary zones. Recesses were seen here too between normal tissue; they revealed primitive tubuli surrounded by concentric connective tissue, and rudimentary glomeruli. The inflammatory changes were most marked around these dysplastic areas.

Case 19. R. L., a boy (No. 4477/58) with a birth weight of 3,400 g. The child was cyanotic and had poor respiration ever since birth. He was admitted for respiratory difficulties and died at the age of 1 day.

Autopsy revealed a lowered air content in the lungs, the consistency of which was firm. Microscopic examination performed later showed copious hyaline membranes in the alveoli as the cause of death. There were two cysts 3 cm in diameter containing clear fluid where the right kidney should have been. There was no renal tissue between or around the cysts. The ureter, with the lumen missing in the upper third, opened normally into the bladder. The left

formed on the day of admission. A roentgenogram taken 2 days postoperatively revealed no air in the intestines.

Laparotomy and right-sided *nephrectomy* were performed at the age of 8 days. On the right there was a multicystic kidney in which no renal parenchyma could be demonstrated. The hilar vessels were thin and a couple of veins drained beyond the upper pole. The ureter appeared normal; it was tied, likewise the vessels. On palpation the left kidney felt lobulated but of normal size. The stomach and the duodenum were wide, pouchlike; the small intestine appeared otherwise normal. The largest, anteriorly situated, cyst of the cystic kidney had apparently pressed the duodenum closed, thus obstructing the passage. — The patient died 2 days after the second operation with symptoms of pneumonia and pleural empyema.

Microscopy of the excised kidney: The samples showed small areas of normally organised renal tissue. The capsules of the glomeruli were thick. Their epithelium was proliferative. The proximal tubuli were dilated in the areas corresponding to the cortex and the epithelium lining them shallow, cuboidal. They were full of colloid material here and there. The tissue between the large cysts was chiefly collagenous connective tissue in which there was a rich capillary network and thickwalled hyalinised blood vessels. The intercystic tissue also revealed islets of embryonal connective tissue concentrically around the primitive tubuli. Some of the tubuli were cystically enlarged. Their epithelium was ciliated and it proliferated thrusting polypoid projections into the cavity. In addition cartilaginous islets encircled by connective tissue, and lymphatic follicles were seen. The large cyst cavities were lined with cuboidal epithelium. The cyst wall consisted of collagenous connective tissue and rudimentary glomeruli with cystic Bowman's capsules.

Case 17. S. A. J., a boy (No.1152/58) who was the first child of his mother of 32. At the maternity hospital the mother was found to be suffering from nephropathy. Her blood pressure was 170/110 mm Hg. The child was in a state of deep suspended animation at birth.

Upon admission to hospital the patient was cyanotic, slightly icteric; a nodular tumour extending to the iliac fossa was palpable on the left of the median line. The child weighed 2.500 g, height 48 cm. Direct bilirubin was 0.5, indirect 15.5. The Meulengracht was 1: 100, erythroblast count 20/100. The blood group of the mother was not known. Although the Coombs test from the child's blood was negative exchange transfusion seemed indicated. On performing the exchange transfusion the umbilical vein was perforated and laparotomy was consequently performed. The left kidney was the size of an egg; its lower portion consisted of a major cyst but it was otherwise multicystic. The right kidney appeared normal. The child died at the age of 5 days.

Autopsy revealed intraventricular bleeding in the brain to be the cause of death. The child was externally well developed. The testicles were in the inguinal canal. There was a small clot around the site of perforation of the umbilical vein. The spleen and the liver were large. They showed profuse blood formation microscopically. The testicles were of normal size. The left kidney consisted of c. 20 cysts. The left ureter terminated in a blind pouch at the level of the promontory. The right kidney was markedly hydronephrotic, the pelvis was wide, the interior surface pale and there was a stricture at the junction of the ureter and the pelvis.

Microscopic examination of the kidneys: The left kidney showed between the cysts small islets of normally organised renal tissue. The glomeruli were lined with cuboidal epithelium. Bowman's capsules were cystic. The proximal tubuli were wide, cystic and contained here and there a material reminiscent of colloid. Their epithelium was flat, endothelial. The tissue between the cysts consisted of collagenous

Incidence

According to the most recent review (Coppridge & Ratliff), the unilateral multicystic kidney seems to be very rare, only 31 cases being reported in the literature. Moore (1957) had 5 cases among 58 495 hospital admissions (0.009%). Bell (1946) found 11 unilateral cystic kidneys among 32,360 autopsies (0.03%) and 64 bilateral cystic kidneys in the same material (0.2%). Our 19 cases were found during 12 years among roughly 32,000 pediatric hospital admissions (0.05%) and the 15 cases in which autopsy was made were among 2,900 autopsies (0.5%) performed during the same period. Of our material, 12 cases were found during the last 3 years among roughly 14,000 hospital admissions (0.085%) and 900 autopsies (1.3%). This is in accordance with Grob's experience that »the aplastic cystic kidney» is the most usual form of cystic kidney in infancy. Similarly, during 20 years Longino & Martin found 15 infants with hypoplastic cystic kidney among 32 infants admitted because of abdominal mass to the Boston Children's Hospital. The seemingly rare occurrence might depend of the variety of names under which multicystic kidneys are reported and filed. »Undoubtedly many more cases will be added when and accurate definition and classification of renal structural anomalies has been established» (Abeshouse).

Of the 27 unilateral multicystic kidneys reviewed by Menashe & Smith (1957), 22 have been in the pediatric age group. Potter (1952) found multiple cysts in the kidney of a fetus weighing 35 grams, at 14 weeks gestation. The oldest patients, on the other hand, we have found in the literature were 70 (Spence) and 78 years old (Abeshouse). The age in our cases at death or at clinical diagnosis varied from 1 hour to 1 year 8 months. Our Case 9 was a premature female infant weighing 980 g.

The vast majority of multicystic dysplastic kidneys reported have been unilateral, in accordance with the accepted definition (Schwartz; Ravitch & Sanford; Spence *et al.*). If bilateral cases have occurred, they have been treated under polycystic kidneys (Potter; Hooper). Grob gives some hint of the possibility of the bilateral occurrence in writing that »aplastic cystic kidney» is mostly unilateral. We have been able to find only 2 reports on bilateral multicystic kidneys in infants (Longino & Martin; Hooper). Among our 19 patients, one female had bilateral multicystic kidney (Case 7) and another had a multicystic dysplasia of the lower pole in the contralateral kidney (Case 18).

Both sexes and both sides are said to be affected equally. In our material, 7 were females and 12 were males. The lesion was on the left side in 4 females and 5 males, on the right side in 2 females and 6 males. In addition, 1 female (Case 7) and 1 male (Case 18) had bilateral lesions.

kidney was 3 × 2 × 1 cm and of normal shape. Several scar-like depressions were seen on its surface. The margin of the cortical and medullary zone was sharp. The pelvis was small. The open ureter emptied into the bladder in the normal manner. The bladder was of normal size. The wall was thick and the urethra open. The testicles were in the scrotum.

Microscopic examination of the kidneys: The cysts corresponding to the right kidney had thin walls. The walls consisted of collagenous connective tissue and smooth-muscle fibres. There were some rudimentary glomeruli in the walls. The cysts were lined with shallow cuboidal epithelium. The connective tissue between the cysts was of varying density. It showed small islets of immature embryonal connective tissue and cartilage. The samples contained no normally organised renal tissue.

There were numerous dysplastic areas in the left kidney. There were rudimentary glomeruli with cystic Bowman's capsules and primitive tubuli surrounded by immature embryonal connective tissue. The structure of the parenchyma between the dysplastic areas was normal for the age.

Microscopic Description.

Stroma. The most typical finding of multicystic kidney is the increased amount of connective tissue, which is far more abundant than in the usual congenital polycystic kidney (Potter; Menashe & Smith). This connectice tissue may be fibrous (Abeshouse), or loose and embryonic in type and richly supplied with vessels (Staemmler 1957). This stroma may contain primitive renal elements (Williams) or cartilage and smooth muscle (Staemmler). In the cyst walls the connective tissue is denser (Staemmler).

In our cases, the density of the stroma varied considerably in different parts of the mass. In nearly all cases islands of immature connective tissue were found which resembled the undifferentiated connective tissue found in Wilms' tumours. Around the primitive tubuli this was concentrically arranged, and intermingled with smooth muscle fibres. In the stroma, in all cases but two a rich capillary network (Marshall 1953) was seen, but mostly also thick-walled arteries. Moreover, in most cases small areas of normally organized kidney tissue, small bits of cartilage, primitive tubuli and a few scattered primitive glomeruli were also present in the stroma.

The connective tissue of the »hypoplastic cystic kidney» is said to be rich in blood vessels (Staemmler), and the multicystic kidney in adults has been found to contain contracted blood vessels (Abeshouse), thick-walled vessels (Herczec *et al.*), numerous small blood vessels (Oehlecker 1951), or numerous arteries, veins and capillaries (Klosterhalfen; Kempf; Funfack 1956). Dysplastic kidneys often contain angiomatous areas (Williams). In the scars of the renal cortex a sinusoidal vascular network has been noted very frequently (Marshall 1956). In our multicystic kidneys (Figures 1, 9 and 10), in nearly all of them (except Cases 5 and 11), a rich capillary network was seen similar to that described by Marshall (1953) as foetal structures in pyelonephritic kidneys. In addition, thick-walled arteries were seen in almost every case (except Cases 9, 13, 14 and 19).

Lymphocytic infiltrations have been found in neonatal kidneys in the absence of infection and have been considered to be associated with haematopoiesis (Marshall 1953). Abeshouse put forward the opinion that round cell infiltrations are indicative of chronic infection. In adult multicystic kidney, when present (cases of Cicchino, and Herczeg *et al.*), they may, of course be

Macroscopic Findings

All the kidney is replaced by an irregular mass composed of many cysts varying in size and number (Ravitch & Sanford; Williams). The cysts are held together by loose connective tissue like a bunch of grapes. No normal renal parenchyma can be seen except for an occasional nubbin (Spence *et al.*). One case with a multicystic upper pole of a double kidney has been reported (Pagel 1958). In our material, the number of the cysts in the bunch varied from 2 to 20, but as many as 36 have been reported (Coppridge & Ratliff). The walls of the cysts were thin, and macroscopically we could not distinguish normal renal parenchyma, except in Case 18 in the contralateral kidney.

The cystic mass is usually found in the kidney area. Similarly, the location of the cystic mass in our cases corresponded to the normal location of the kidney, with one exception. In Case 4 the cystic mass was situated dystopically at the pelvic brim. Priesel (1956) has reported a similar case. A multicystic lesion in a crossed ectopic kidney has been reported by Herczeg *et al.*

The ureter has been found to be normal or smallish in a few instances, but characteristically it is said to be absent, rudimentary or atretic (Abeshouse; Weinberg, O'Connor & Sengler 1956, Spence *et al.*, among others). Even the ureteric orifice may be absent (Williams) or ectopic (Grob). Renal pelvis and calices likewise may be atretic (Williams). In most of our cases at least some ureter was present from the bunch of cysts to the bladder; the ureter was fairly normal in 8 cases, and atretic or occluded in 7 cases. In Case 17 the ureter ended as a blind pouch some distance below the bunch, and in Case 10 the ureter was totally absent. In 2 cases no mention of the ureter was made. In none of our cases were any renal pelvis or calices detected (except in Case 18 in the contralateral kidney).

The blood supply of the multicystic kidney is variable (Spence; Spence *et al.*). Some operators have noticed a vascular pedicle (*e.g.* Ravitch & Sanford) and some multiple small vessels (Klosterhalfen 1958), no normal vascular pedicle (Abeshouse) or no vascular pedicle at all (Hennig; Cicchino 1951, Herczeg *et al.*). Once, during translumbar aortography, a renal artery of fairly normal calibre was seen to contain a cylinder of cheesy material (Maluf 1958). In our cases, the hilar vessels were normal in 3 (Cases 8, 11 and 15) and anomalous in 2 (Cases 5 and 16). In the others, no mention of the hilar vessels was made.

kidneys at least some scattered glomerular structures were found (Figures 2, 4, 8 and 9), even in the absence of the corresponding ureter or in cases of its obliteration. In most kidneys, in addition, microscopic areas of normal organization could be seen, in Case 14 even a macroscopically detectable knob. Here, the glomeruli were infantile, sometimes hyaline. Bowman's capsule was thick, and the covering epithelium cuboidal. In some places epithelial proliferation was seen. Outside the areas of normal organization only scattered atypical, foetal or rudimentary glomeruli were seen embedded in the stroma. The capsule was mostly dilated and the glomerulus itself lay collapsed inside. The capsule, in many instances, was filled with colloid-like material. In serial sections, in some of the cases, these glomeruli were not found to communicate with the large cysts, but had a short tail, which we interpreted as a proximal tubulus.

Tubular structures. In most of the reported cases of multicystic kidneys at least some tubular structures have been found, even in some of the adult cases (Kempf; Klosterhalfen; Spence, among others). In the areas of normal organization the tubuli have been fairly normal (Boggs & Kimmelstiel), slightly dilated or embryonic in type (Spence). Similarly, in the abundant connective tissue scattered tubular structures have been found (Froboese 1952). The epithelium has been cylindrical (Froboese; Lipton & Scordamaglia; Ravitch & Sanford), cuboidal or flat (Klosterhalfen; Ravitch & Sanford), depending on the dilatation of the tubuli (Lipton & Scordamaglia; Ravitch & Sanford). Some of these tubuli have been interpreted as convoluted tubuli (Cicchino *et al.*), some as connecting tubuli (Klosterhalfen; Spence). It has been pointed out (Kempf) that it is difficult to decide, owing to the undifferentiated nature of the tubuli, whether their function is excretory or secretory.

More often, however, primitive tubular structures of an entirely different type have been described in multicystic kidneys (*e.g.* Ravitch & Sanford). Embedded in primitive connective tissue there are tubuli lined with a high pseudostratified columnar epithelium surrounded by a concentric arrangement of primitive connective tissue and smooth muscle. Similar structures have been found in renal hypoplasia with or without obliterated ureter (Williams) and in hydronephrotic kidneys (Fink, Garlick & Stein 1957). In kidneys with ureteral duplications these structures have been regarded as a sign of dysplasia (Ericsson & Ivemark 1958, Williams). Further, similar structures have been found in foetal kidneys and in pyelonephritic kidneys, and called persistent foetal structures (Marshall 1953). They have been considered to be remnants or similar to Wolffian ducts (Ericsson 1954), because their histological structure tallies with that of residual Wolffian structures elsewhere in the body (Ericsson & Ivemark). When seen in an adult human kidney, they have been called developmental remnants (Johnson & Anderson 1953). Ductuli resembling the paroophoron were seen at the

due to infection. In infant cases of multicystic kidney (Boggs & Kimmelstiel 1956, Menashe & Smith) they are probably not caused by infection, for they have been seen in newborn kidneys (Marshall 1953) and in the scars of the renal cortex without signs of infection (Marshall 1956). Lymphoid follicles should be considered to be dysplastic tissue (Marshall 1956). We found lymphoid follicle-like structures in 6 cases (Cases 1, 7, 11, 13, 16 and 18). In Case 7, where the patient died at the age of 4 hours, and in Case 13, where he was operated on at the age of 7 days, these lymphoid accumulations were in all probability not caused by infection.

Multicystic kidney often contains small foci of cartilage (Staemmler; Potter; Spence; Ravitch & Sanford). Bigler & Killingsworth (1949) considered the cartilage found in hypoplastic and cystic kidneys to be the result of metaplasia of the embryonic connective tissue. Dysplastic kidneys may contain masses of cartilage (Williams); even in the normal neonatal kidney cartilage has been found (Marshall 1953). In 9 of our 17 multicystic kidneys examined histologically foci of hyaline cartilage were seen (Fig. 9). In adult cases, however, cartilage has not usually been found. We therefore consider the primitive cartilage as a dysplastic structure.

Cysts. The walls of the larger cysts are reported to be composed of fibrous tissue, the thickness of which varies. The epithelial lining is low cuboidal or flat (Abeshouse; Spence), or the epithelium is absent (Kempf). Localized or diffuse degenerative (hyaline and calcific), and metaplastic (cartilaginous and osseous) changes have been described in the walls of the cysts in elderly patients (Kempf; Hennig; Abeshouse), more seldom in infants (Abeshouse). In fact, we have been able to find only one reported case with calcification in the cyst wall in an infant (Menashe & Smith). In some cases, smooth muscle has been found in the cyst wall in adults (Hennig).

In our cases (Figures 1, 2, 3, 4 and 5), the walls of the larger cysts were composed of rather dense, more or less collagenous connective tissue. In nearly all cases, at least some smooth muscle was seen in the cyst walls. The epithelial lining varied in different cases and cysts, from high cuboidal to flat endothelial. In addition, in many cases there were smaller cysts lined by pseudostratified epithelium. The walls of these cysts were made of concentrically arranged embryonic connective tissue with smooth muscle fibres.

Glomeruli. In some cases, especially in adults, no glomerular structures have been seen (Hennig; Kempf; Abeshouse). Little islands of nephrons in different stages of atrophy may be seen (Menashe & Smith), or the rare glomeruli are embryonic or show advanced sclerotic or hyaline changes (Abeshouse). Microscopic areas of normal organization may be visible (Staemmler). Infantile tubular and glomerular structures have been seen in the solid tissue (Spence).

In all of our multicystic dysplastic



Fig. 1. — A multicystic kidney removed at operation.

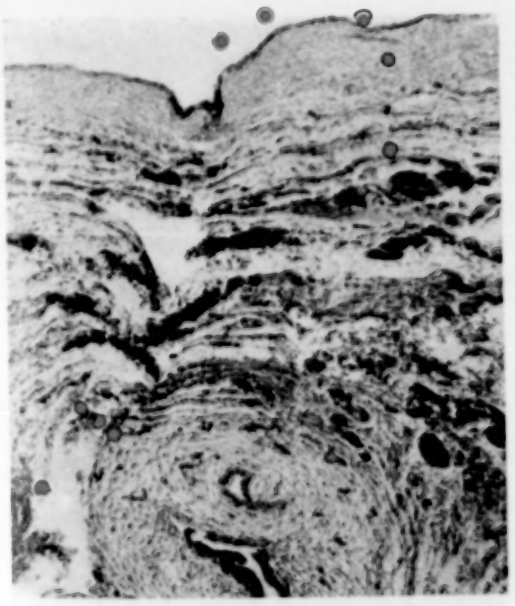


Fig. 2.



Fig. 3.

Fig. 2. — Case 6. Wall of a big cyst which is lined with a single-layered cuboidal epithelium. The wall consists of dense collagenous connective tissue. In the centre the rich vascular network is is clearly seen. A primitive tubulus surrounded by primitive concentrically arranged connective tissue is seen in the lower part of the picture. ×50.

Fig. 3. — Case 11. A cystic cavity lined with cuboidal epithelium on the right. Scattered glomeruli are seen in the richly vascularized stroma. ×100.

hilus of cystic mass in the case of Ultzmann (1951).

In our cases (Figures 6, 7, 10, 11, 12, 13 and 14), in the areas of normal organization a fairly normal tubular pattern, corresponding to the age of the patient, was seen. Mostly, the epithelial lining was cuboidal. Often, some dilatation in the tubuli was seen, and then the epithelium was somewhat lower, This especially concerned tubuli which we considered to be proximal ones. In only a few instances were tubuli which we considered to be collecting tubuli seen (Cases 5, 8 and 11). In the stroma, the most usual type was the primitive tubulus, with high epithelium and concentric arrangement of embryonic connective tissue and smooth muscle. Sometimes the epithelium was pseudostratified, protruding into the lumen of the tubulus (Cases 9, 15 and 16). On many occasions, the epithelium was stereociliated (Cases 4, 5, 6, 7, 10, 13, 14, 15 and 18). In Cases 10 and 14, these tubuli were considered to be epididymis. Similar epididymal tubuli have been seen in »aplastic kidney» (Williams), and in hypoplastic kidney (Cicchino *et al.*). Dichotomous division was seen on many occasions (Cases 9, 14 and 15). In Cases 4 and 10 testicular tissue was visible, the seminiferous tubuli being infantile in type. In the former case, the genitals were found to be normal, in the latter the testis was attached to the cystic mass, as in the case of Howze & Hill (1945).

Ossifications. Calcific changes in the cyst wall have mostly been found in adults (Abeshouse; Hennig; Messerschmidt 1954, Kempf; Funfack, among others), in infants very seldom. In the infant case of Menashe & Smith an occasional calcific area was found. In an infant ageing 4 days, Trillat *et al.* found calcific lamellations in the cystic tissue. In none of our cases could any calcified areas be seen, except some calcific precipitations on very few occasions. Calcifications have not been seen in the newborn kidneys containing dysplastic elements (Marshall 1953). Consequently we regard the calcific changes as secondary and not as a sign of dysplasia.

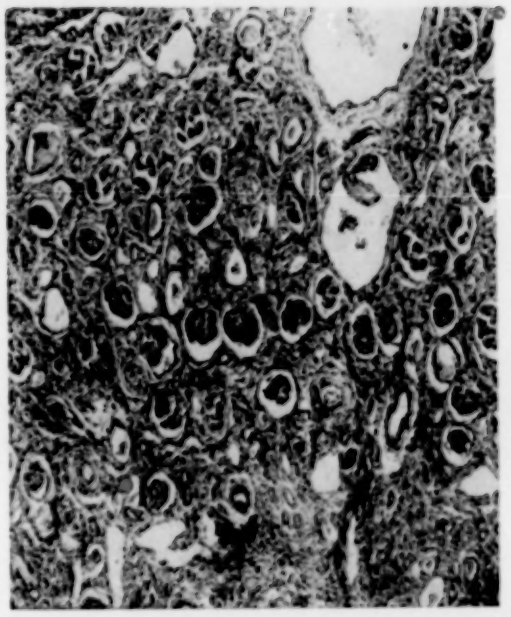


Fig. 8. — Case 14. Normally organized renal tissue. In the the upper part two glomerular cysts are seen. All the capsular spaces of the glomeruli are widened. The tubules are dilated. Some of them are filled with a colloid material. ×50.

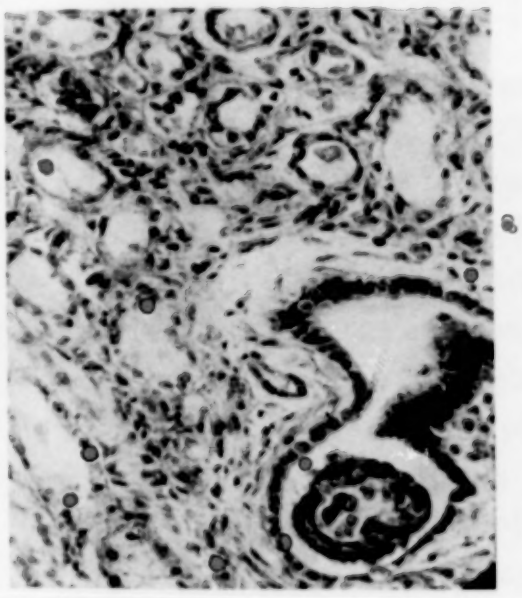


Fig. 9. — Case 14. A rudimentary glomerulus. The Bowman's capsule is lined with a high epithelium. ×200.

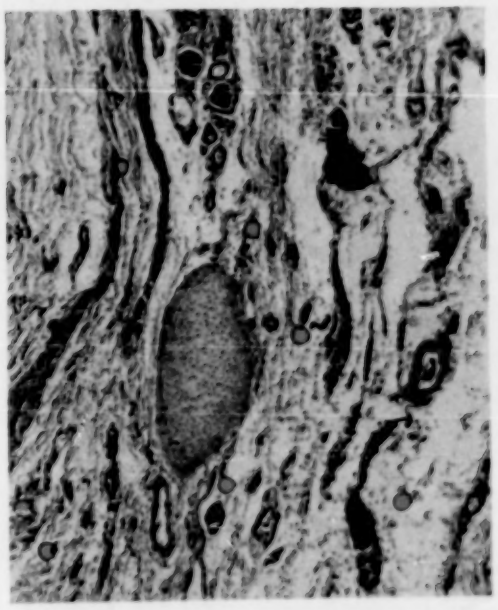


Fig. 10. — Case 5. Loose intercystic tissue in which a piece of cartilage is seen. The tissue is richly vascularized. A group of glomeruli and tubules is found on the right. In addition, scattered single glomeruli are seen. ×100.



Fig. 11. — Case 7. Blood-filled capillaries and thick-walled vessels. At bottom a group of collecting tubules and scattered amongst them a few primitive tubules, lined with a polypous superciliated epithelium. ×100.

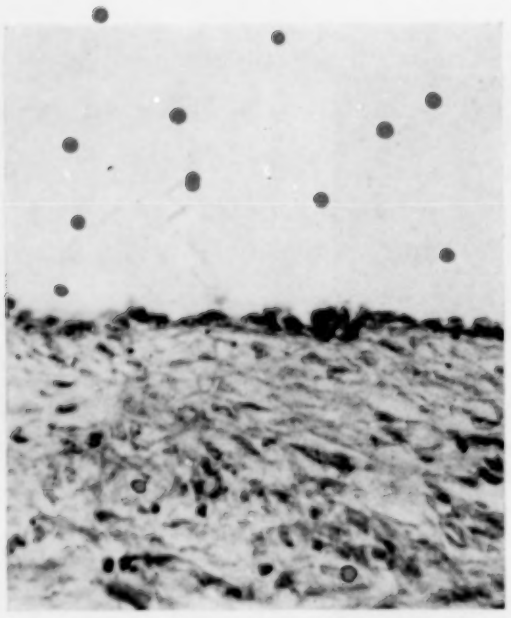


Fig. 4. — Case 12. Wall of a big cystic space, lined with a flattened low epithelium. The wall consists of collagenous and smooth muscle fibers. ×315.



Fig. 5. — Case 1. Two cysts, both lined with cuboidal epithelium. In the wall of the other cyst rudimentary glomerular structures and dilated tubules are seen. ×100.



Fig. 6. — Case 3. An area with small cysts all lined with cuboidal epithelium. The walls of the cysts and the intermediate tissue consists of primitive connective tissue. ×100.



Fig. 7. — Case 13. Wide primitive tubules surrounded by concentrically arranged connective tissue and smooth muscle. ×100.

Associated Anomalies

There is a divergence of opinion concerning associated anomalies in connection with multicystic dysplasia of the kidney. Those reporting adult cases assert that there are no other congenital anomalies (Kempf; Funfack, among others) and the same has been said to be true of infants (Weinberg *et al.*). In 10 of the 27 reported cases, however, Menashe & Smith found abnormalities of the ureter and the renal pedicle, and in 2 instances an undescended testis was adherent to the cystic mass. Multiple dysplastic scars in the renal cortex have been commonly found in association of congenital kidney anomalies (Marshall 1956). Anomalies outside the urogenital tract may be present (Grob; Staemmler). In fact, in cases in which operation or autopsy has not been done, the exclusion of other malformations cannot be regarded as very well founded (Herczec *et al.*).

Of our cases 15 were autopsied, and the remaining 4 were operated on, after adequate general and urological preoperative examination. Consequently various associated congenital anomalies, many of which were incompatible with life, were found in large numbers.

Anomalies confined to the contralateral kidney in addition to the multicystic side were found in 4 cases: agenesis of the contralateral kidney (Case 6); hydronephrosis (Case 11); multilocular cystic kidney (Case 18); dysplastic kidney (Case 19).

In addition to multicystic kidney there were other anomalies both in and outside the urinary system in 3 cases: bilateral multicystic kidney, double uterus, and cloaca (Case 7); agenesis of the contralateral kidney, patent urachus, absence of the contralateral testis, the ipsilateral testis being attached to the cystic mass, anal atresia, and bilateral dislocation of the hip (case 10); hydronephrosis on the contralateral side and bilateral undescended testis (Case 17).

Anomalies only outside the urogenital organs in association with multicystic kidney were found in 7 cases: oesophageal atresia (isolated) in 2 cases (Case 2 and 16); oesophageal atresia, ventricular septal defect of the heart, transposition of the aorta and the pulmonary artery, open ductus arteriosus, and accessory spleen (Case 4); oesophageal atresia, anal atresia with a rectovaginal fistula, and multiple spleen (Case 12); oesophageal atresia, and bilateral defect of the radial and first metacarpal bones (Case 13); isolated patent ductus arteriosus (Case 15); accessory spleen (Case 14). Oesophageal atresia was the commonest of the concurrent malformations, being present in 5 cases.

No associated anomalies were noted in 5 patients (Cases 1, 3, 5, 8 and 9).



Fig. 12. — Case 10. Two primitive tubules are seen at the bottom of the picture. They are surrounded by a concentrically arranged layer of primitive connective tissue. On the right large blood-filled vessels. ×100.

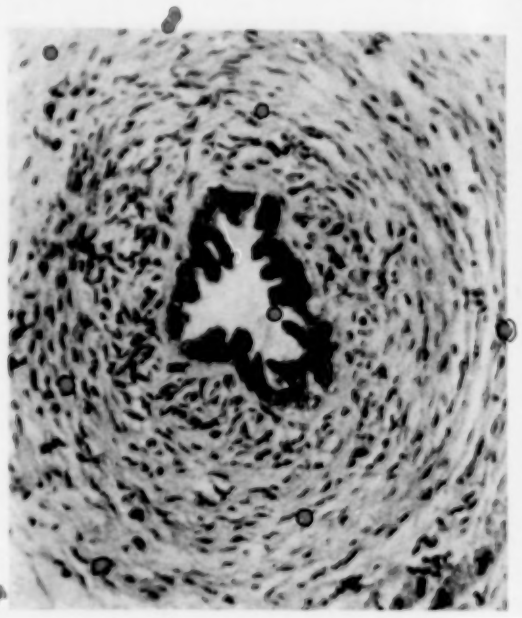


Fig. 13. — Case 12. A primitive tubulus lined with a polypous superciliated epithelium and surrounded by a thick layer of embryonic connective tissue. ×200.

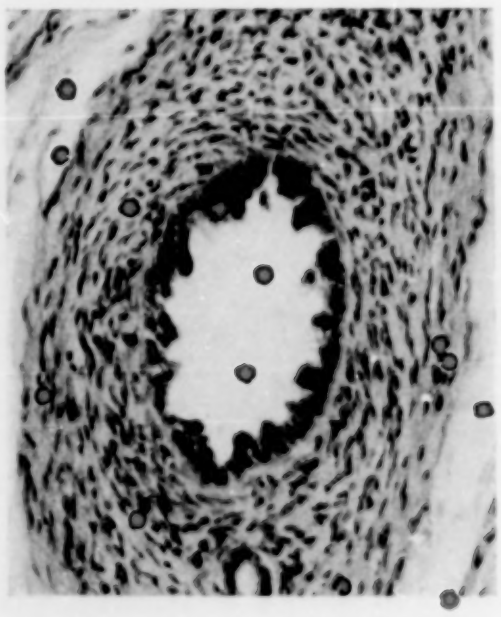


Fig. 14. — Case 13. A primitive tubulus. ×200.



Fig. 15. — Case 8. A primitive tubulus surrounded by undifferentiated connective tissue. The epithelium is superciliated. ×200.

ler). The stimulus from the ureteral bud is essential for glomerulus and tubulus formation from the metanephrogenic tissue, and no case has ever been reported in which the renal parenchyma existed without a ureter (Potter). If the ureter and the renal pelvis were arrested in some phase of their development, the mass capping the tip of the ureter in such an instance is not a kidney and does not contain glomeruli or the proximal tubules of the nephron (Cicchino). On the other hand, there are no descriptions of a normally developed ureter or a ureter which had divided into the kidney pelvis without renal cortical tissue (Nierenrindengewebe, Staemmler). When a ureter is present, there is always some semblance of kidney tissue, although it may be only a rudimentary mass weighing a few milligrams (Potter), and the aplastic kidney thus formed may contain glomeruli and tubuli in varying quantities.

The arteries of the mesonephros develop as numerous branches from the aorta in the course of appearance of new mesonephric nephrons. These branches develop and atrophy corresponding to the developing caudal and atrophying cranial mesonephric nephrons. The venous blood from the mesonephros drains through the developing cardinal and sub-cardinal veins (Patten). From its original pelvic position the kidney moves cranially while still in its formative stage (Bremer). The actual ascent of the kidney is only 3—4 somites, and is mainly due to the straightening of the spinal curves and to the growth of the vertebral bodies (Bremer). During its travel the kidney receives its main arterial supply from the mesonephric arteries, making new regional connections and losing old ones (Bremer). The final renal artery develops from an enlargement of one of the periaortic capillary plexuses (Bremer). In other reviews the final renal artery is said to develop from one of the mesonephric arteries (Kempf; Funfack), so that when in its final site the kidney is still supplied by several arteries, one of which remains after the atrophy of the others.

Embryology

The development of the human kidney is usually thought to have three different phases (Potter; Bremer 1957). The pronephros is visible in the beginning of the 4th embryonic week. The earlier pronephric tubuli begin to degenerate before the last ones appear. Vesicles and tubuli continue to be formed in the region caudal to the pronephros and to be attached to the duct. The prolongation of the pronephric duct, called the mesonephric duct, reaches the cloaca at the end of the 4th week. By the 6th week the mesonephros forms a pair of ovoid organs from the level of the heart to the extreme posterior portion of the body cavity (Patten 1948). The mesonephric tubuli mostly degenerate by the 8th week. Some, however, persist in the female as a few vestigial structures (epoophoron and paroophoron) adjoining the gonads. In the male a part of the tubuli persist to form the epididymis (Potter). The mesonephric duct becomes the ductus deferens in the male.

During the 5th week the ureter appears as a bud from each mesonephric duct near its point of entrance into the urogenital sinus. The bud grows cranially and terminates as a blind pouch to form the renal pelvis. The pelvis is partially enclosed by a mass of mesodermal tissue, known as the metanephrogenic tissue or renal blastema (Potter) caudally of the mesonephros, at the level of 2nd and 3rd sacral segments (Campbell). By division and subdivision of the renal pelvis in the metanephrogenic blastema calices and minor calices are formed. From the minor calices several generations of branches arise successively to form the collecting tubuli. At the tip of each collecting tubulus a tubular structure, the uriniferous tubule, is formed. At one end of the latter a glomerulus is formed, whilst the other end unites with the collecting tubulus (Potter; Bremer). Differentiation of the new generations of uriniferous tubuli and glomeruli takes place only as long as the preceding generations assume a definite form (Potter). Normally the collecting tubuli give off about 12 generations of branches. This branching continues until birth or later (Bremer). The metanephrogenic tissue gives rise to an equal number of generations of glomeruli. In the foetal kidney of the latter part of pregnancy various developmental stages of glomeruli can be seen, the youngest near the surface, the functional ones near the pelvis (Bremer).

Usually the differentiation of renal parenchyma from the netanephrogenic blastema is thought to depend on the stimulation caused by the ureteral bud (Potter; Bremer; Campbell; Staemm-

ment or may be secondarily disturbed after normal differentiation.

In conclusion, a rather wide divergence of opinion seems to exist as to the origin and the etiology of the multicystic kidney. This, we think, depends on the fact that most opinions are based on very few observations or on adult cases only. Many observations do not exactly seem to refer to multicystic kidneys, and in some cases no microscopic or postmortem examination has been made.

In discussion on the etiology or origin of the multicystic kidney, the following are the main details used to support the supposed etiology:

1) the ureter, whether present, rudimentary or absent;

2) the blood vessels, whether normal, anomalous, rudimentary or absent;

3) the localization of the multicystic lesions;

4) the absence of other anomalies, especially of testis, epididymis and ductus deferens;

5) the various primitive elements;

6) the function of the anomalous structure.

The ureter. The observation that the ureter is characteristically absent, rudimentary or atrophic (Abeshouse) has been proposed to support the mesonephric (Hennig) or metanephric (Klosterhalfen; Herczeg *et al.*) origin of the malformation. Nowadays, the common conception is still that the formation of the kidney does not take place in the absence of ureteral stimulation (Stæmmler; Ericsson & Ivemark), or that in the absence of the ureter the metanephrogenic tissue does not differentiate (Funfack; Boyden 1932). In many cases, however, including all our cases, glomeruli have been found in the parenchyma even in the instance of total absence of the ureter. The tubular structures resembling a ureter were thought to be remnants of the ureter (Herczec *et al.*) which, after exerting its stimulating effect on the metanephrogenic blastema, had secondarily atrophied or become obliterated (Kempf; Herczec *et al.*; Klosterhalfen). Had secondary atrophy occurred, some atretic ureter, at least, or an atrophied fibrous cord, extending from the bladder to the hilus of the bunch would be expected to remain, especially in the newborn. No trace of a ureter could be found, however, in our Case 17, in which the ureter ended blindly at the pelvic brim, and in Case 10, in which the ureter was totally missing. Similarly, the ureter must have been completely absent in cases in which even the ureteral orifice and the corresponding half of the trigonum were missing (Williams). From these observations we can only conclude that similar multicystic dysplasias do occur in cases of total primary absence of the ureter and in cases where a normal ureter is present. The defective development of the mesonephric, as well as of the metanephric blastema might be capable of producing the multicystic dysplasia of the kidney.

The blood vessels. Missing hilar vessels are adduced as strong evidence in support of the mesonephric origin of the multicystic kidney (Ultzmann;

Etiology

General review. The most popular theories of the etiology of the cystic kidneys are those proposed by Hildebrandt (1894) and Kampmeier (1923). Hildebrandt suggested that metanephric parts of the nephron fail to establish communications between parts derived from the collecting tubuli. Later, the etiology of the multicystic kidney (Spence; Weinberg *et al.*), as well as of polycystic disease of the kidney (Abeshouse) has been explained by this theory. Kampmeier has tried to explain polycystic disease in terms of cystic degeneration of early generations of nephrons. In Spence's opinion this theory fits the »true polycystic kidney». On the other hand, Potter states that this process of cystic degeneration has not been proved. Hepler (1930) produced simple cysts in rabbits by coagulating tubular openings and ligating the corresponding branch of the renal artery. According to Spence, Hepler's theory best explains multilocular cyst formation in the kidney.

Potter, on the basis of her 50 cases of polycystic kidneys, most of which can be considered to be cystic dysplasias (»in which the connective tissue is increased»), found nothing to support either Hildebrandt's or Kampmeier's theory. She suggested 6 different etiological possibilities and did not see any justification for attempting to explain the origin of all types of polycystic kidney on the same basis. Staemmler, too, doubted whether all cystic kidneys have the same pathogeneses.

In the recent reports and reviews of the German literature, comprising mainly adult cases (Klosterhalfen; Funfack; Bibus 1954, Kempf) both pronephric, mesonephric and metanephric origins of the multicystic kidney have been proposed. Abeshouse, however, did not see anything to support the view that these congenital anomalies are due to the defective development of the most primitive kidney from the early embryonic period.

Goodyear & Beard (1948) and Fink *et al.* suggest that the cysts are dilated calices »as a result of failure of union of the primitive ureter and the metanephrogenic blastema». The multicystic condition, however, can in no way be considered as a hydronephrotic process (Spence *et al.*; Abeshouse), although, on the other hand, rather similar changes are often found in infants dying of lower urinary tract obstruction, which may prevent the maturation of later generations of nephrons (Williams). Potter mentions that a part or all of any kidney may be arrested at any stage of its develop-

28.5 days gestation. Organogenesis of the genital ridge and the spleen is at 33.5 days. Concluding from associated anomalies of this kind present in our material it seems probable that the disturbance occurred about at these times. This is supported by the case of Lipton *et al.* in which maternal rubella at 2 months' gestation was the probable cause of multicystic kidney.

The various *primitive structures* in the parenchyma of multicystic kidney, called foetal structures (Marshall 1953), developmental (Johnson & Anderson) or embryonic remnants (Spence), or vestigial structures (Cicchino *et al.*), have usually been understood to be derived from the metanephric blastema or the ureteric bud (primitive tubuli). The similarity of the primitive tubuli to Wolffian duct remnants (Ericsson; Ericsson & Ivemark) or the epididymis (Cicchino *et al.*) might suggest the mesonephric origin of the multicystic mass. At all events, these dysplastic structures are to be considered as persistent foetal tissue and not as secondary changes, because they do occur in the foetal kidney independently of a superadded pyelonephritis and because they are often associated with congenital anomalies (Marshall 1953).

Function. The content of the cyst fluid in the multicystic kidney (Abeshouse; Staemmler) and in the simple, multiple and multilocular cysts (Glaser 1952) is said to be non-urinous, although some writers (Weinberg *et al.*; Coppridge & Ratliff) describe the fluid obtained from a cyst as being urine-like. In some of the cases of our material (Cases 8, 14, 15 and 16) the cyst fluid was analyzed in regard to some of its components (Parkkulainen & Visakorpi 1959). In one case, moreover, the amino acid content of the cyst fluid was determined. It was concluded that the cyst fluid, although very variable in composition, might be the product of glomerular filtration, especially in the case in which the amino acid taurine was present in large amounts. As taurine is supposed to develop only in the presence of functional renal parenchyma, it was concluded that at least some of the cysts are connected with functioning nephrons. It is impossible to say whether these nephrons are metanephric or mesonephric, for at some stage of development mesonephric and metanephric nephrons have a similar function (Patten).

Conclusion on the etiology. On the basis of the facts reported in last 6 paragraphs it is concluded that the multicystic dysplastic kidney is a congenital anomaly caused by disturbance in the development of nephrogenic tissue during the early phases of foetal life, *i.e.* during the first 2 months.

Hennig). It is true that in most adult cases no hilar vessels have been noticed, partly because secondary changes may have taken place (Campbell). But even in adults a renal artery of fairly normal calibre has been seen (Maluf). In infants, obviously, many small vessels may escape notice. In some of our cases the hilar vessels appeared more or less normal, or were smaller than normal. This strongly supports the metanephric origin of the multicystic bunch. The presence of many small arteries at the hilus (Klosterhalfen), on the other hand, does not militate against a metanephric origin. It is believed that the metanephros, during its cranial migration, derives its blood supply directly from the aorta like the mesonephros (Funfack) or from the mesonephros (Bremer). Even in its final site the metanephros usually has many arteries, one of which develops into the final renal artery with atrophy of the others (Kempf). Hence it must be assumed that only the existence of normal hilar vessels affords reliable evidence of the metanephric origin of the cystic lesion. Secondarily atrophied or anomalous renal vessels do not exclude either a mesonephric or a metanephric origin. In both instances a similar macroscopic and microscopic picture has been seen in the multicystic mass.

The localization of the cystic mass in the normal kidney area at the level of upper lumbar vertebrae has been thought to support the mesonephric (Hennig) or metanephric (Bibus) origin of the lesion. There are, however, a few observations on the cystic mass situated dystopically at the pelvic brim (our Case 3, the case of Herczec *et al.*). The metanephros is said to develop at the level of 2nd—5th sacral segments (Funfack) only to move upwards later. These two cases might support the metanephric origin of the lesion, but the localization within the normal kidney area does not exclude either possibility of origin, especially because the pathological picture in the dystopic kidney was similar to the others.

Association of other congenital anomalies has been disclaimed in some reviews. Especially the presence of normal gonads, epididymis and ductus deferens has been alleged to suggest a mesonephric (Hennig) or metanephric (Kempf; Funfack; Klosterhalfen) origin of the multicystic lesion. In some reviews the cases in which associated anomalies have been present have been excluded from this entity (Funfack; Klosterhalfen). In other reviews, associated anomalies have been found (Weinberg *et al.*). In our material a large number of associated anomalies both in and outside the urogenital tract were present. Independently of the associated anomalies, the gross and microscopic structure of the cystic lesions was similar in all our cases. We think that the presence of associated congenital anomalies suggests the malformative nature of the multicystic lesion but does not reveal anything about the origin. However, the associated anomalies may give some hint as to the stage at which a primary disturbance occurred. According to Rugh (1958), the organogenesis of the gastrointestinal tract and its derivatives and of the meso-metanephros falls at

Nomenclature and Definition

In the literature a large number of names have been given to the congenital cystic kidney deformity described in this paper. The term most generally accepted is congenital unilateral multicystic kidney (Schwartz; Ravitch & Sanford; Spence). In our definition we have discarded the word »unilateral» because we have 2 bilateral cases in our material. The bilateral cases reported by Longino & Martin and by Hooper, showed the same microscopic picture on both sides. This is also true in our own cases.

Baggenstoss (1951) has suggested the term dysplasia to disclose the presence of primitive renal elements and tissues foreign to the normal kidney. We have seen these primitive elements (primitive connective tissue with smooth muscle, primitive glomeruli, primitive tubuli, capillary network) in all our multicystic kidneys. Therefore we should like to add this word to Schwartz's definition as the noun »dysplasia», which is indicative of the early disturbance in the development of the foetal kidney. This anomaly is undoubtedly congenital.

We should like to preserve the word multicystic because it is very descriptive of the macroscopic appearance of the deformity.

In accordance what is said above, our definition will be as follows:

Congenital multicystic dysplasia of the kidney, as a sign of an early disturbance in the development of the foetal kidney, in microscopic examination shows various primitive renal elements. Macroscopically it is composed of cysts varying in size and number. Usually the cystic mass is found in the kidney area, but it may lie dystopically. The cysts are held together by loose connective tissue. The hilar vessels may be normal, anomalous or absent. The ureter may be normal, anomalous or rudimentary, and only rarely it is totally absent. The renal pelvis is characteristically absent. At urography, there is no excretion on the diseased side, as a rule. Usually other congenital anomalies are present, many of which are incompatible with life. The deformity is mostly unilateral, but may be bilateral, in which case both kidneys show the same microscopic picture. No familial tendency or heredity has been noted either in the literature or in our material. At a later age secondary changes, especially calcification, may appear.

»*Multilocular cystic kidney*». A great deal of confusion seems to exist concerning multilocular cysts and multicystic kidneys. Both terms have been used to describe pathologically and clinically similar cases (Menashe & Smith). Campbell does not mention multicystic kidney, but under the heading of multilocular cystic kidney he refers to Schwartz's case of, in our opinion, multicystic kidney. Others

Pathogenesis

The formation of tubuli in the renal blastema begins independently of the ureter. At the other end of a tubulus, of glomerulus is formed. Despite failure of the uriniferous tubule to establish union with the collecting tubule (Hildebrandt), glomerular function will continue (Patten). Owing to the high elasticity of the foetal tissues, the blind end of the tubule may be dilated to enormous proportions. This accumulation of urine still continues in postnatal life, as proved by analysis of cyst fluid in cases with multicystic dysplasia of the kidney (Parkkulainen & Visakorpi). The clinical observations that the multicystic mass grows after birth (Froboese) support this postnatal functioning of cystic nephrons. Sooner or later the increasing inelasticity of the tissues causes atrophy of the secreting nephrons. Consequently in adult life the cyst fluid is probably non-urinous (Abeshouse).

Classification of Congenital Cystic Dysplasias of the Kidney

According to the above-mentioned considerations, our principle of classification will be based on the appearance of the primitive or dysplastic renal elements in the cystic kidney. The subordinate grouping may be done according to the macroscopic appearance, which at the same time is also a kind of measure of the severity of the involvement. In multicystic dysplasia the whole kidney parenchyma consists only of cysts and dysplastic structures. In multilocular cystic dysplasia only one part of the kidney is involved, the rest of it consisting of fairly well functioning renal parenchyma. In focal cystic dysplasia (simple renal cysts) only one or a few dysplastic nephrons contribute to the cyst formation, and there is no impairment of renal function unless secondarily caused by pressure. Of course, there are a great many intermediate forms, *e.g.* »multiple multilocular» cystic dysplasias. So this classification chiefly takes into account the clinical manifestations and requirements as well. In the following table our classification is presented together with the synonyms used in the literature for each particular subordinate group.

TABLE

CLASSIFICATION OF CONGENITAL CYSTIC DYSPLASIAS OF THE KIDNEY

OUR CLASSIFICATION	SYNONYMES USED IN THE LITERATURE
1) FOCAL CYSTIC DYSPLASIA = solitary renal cysts, single or multiple	Einzelzysten, (Staemmler 1957); die solitäre Nierenzyste (Grob 1957); simple or solitary renal cyst (Spence *et al.* 1957); simple serous (solitary) cysts (Williams 1958) ;solitary renal cysts (Campbell 1954).
2) MULTILOCULAR CYSTIC DYSPLASIA	Multilocular renal cysts (Spence *et al.* 1957); true multilocular cysts of the kidney (Powell *et al.* 1951); multiloculare Nierenzysten (Grob 1957); multilocular cysts (cystadenoma) (Williams 1958).
3) MULTICYSTIC DYSPLASIA	Polycystic disease in which the connective tissue is increased (Potter 1952); die aplastische Cystenniere (Grob 1957); die hypoplastische Zystenniere (Staemmler 1957); congenital multi'ocular cysts (Campbell 1954); kystes congénitaux multiloculaires (Lauret 1956); unilateral multicystic kidney (Ravitch & Sandford 1949); multilocular cystic disease (Menashe & Smith 1957); metanephric cystic tumour, unilateral polycystic disease, retroperitoneal cysts (Moore 1957); renal aplasia with calcified cystic degeneration (Abeshouse 1956); hypoplastic multicystic kidney (Longino & Martin 1958); Knollenniere (Bibus 1954); Nierenblastemcysten (Kempf 1956, Gütter & Hermanek 1957).

(Powell *et al.*; Spence) described very exactly multilocular cystic kidney and separated it very definitely from multicystic kidney both clinically and pathologically. In the cases of Powell *et al.*, however, similar dysplastic structures (smooth muscle, cellular fibrous tissue, numerous capillaries, dilated primitive tubuli) were described as in our cases. Similarly, Boggs & Kimmelstiel admitted that in the 1st case of their report, a »multilocular cystic nephroma», similar embryonic connective tissue and tubular anlagen were found as in their 3rd case termed as »multicystic disease». According to Spence's definition the multilocular cystic kidney does not seem to differ very much from the multicystic kidney except that in the former the anomaly is limited to one part of the kidney only.

In this material we have had only one case of »multilocular cystic kidney» (Case 18). In this case the cystic dysplasia was confined to a part of one kidney, the other kidney being multicystic in appearance. In both kidneys microscopic examination showed exactly the same dysplastic structures as we have described above. We do not doubt that the etiology and pathogenesis of the malformation are the same in both kidneys. Consequently we should like to include the »multilocular cystic kidneys» under the cystic dysplasias of the kidney.

Solitary renal cysts have not been observed in our material, but they have also been reported to occur in infants (Chalkey & Sutton 1943, Grob), although they are usually found in adults (Williams; Sirola 1957). According to Campbell the simple renal cyst and multilocular cyst of the kidney »undoubtedly have same etiology». Multilocular cysts are said to have much more in common with the simple cysts than with the multicystic kidney (Williams). Glaser and Spence *et al.* classify under simple cysts single, multiple and multilocular cysts. In some of the cases of simple renal cysts reported by Sirola primitive elements (smooth muscle, primitive tubuli) were seen. In addition, 2 out of 9 adult cases showed associated congenital anomalies. Consequently, we think that simple (solitary and multiple) renal cysts have the same etiology as multicystic dysplasia of the kidney, and therefore we include them under kidney dysplasias.

Congenital polycystic disease is said to be a well defined entity characterized by diffuse involvement of both kidneys by innumerable cysts (Spence *et al.*; Williams). However, most of the cases reviewed by Potter are, in fact, polycystic kidneys, »in which the connective tissue is increased». The latter contain primitive structures (Potter, fig. 393, p. 373) similar to those seen in our multicystic kidney dysplasias. Therefore these should be classified under cystic dysplasias of the kidney. It is possible that there exists, in addition, the »true polycystic disease» (Spence) or »the polycystic disease, in which the connective tissue is normal» (Potter) and which does not contain any of the primitive dysplastic structures mentioned above and therefore does not belong to the group of cystic dysplasias.

Treatment and Prognosis

In cases of multicystic dysplasia of the kidney, nephrectomy is the only treatment possible (Spence *et al.;* Grob, among others). In infants, the operation must be performed without delay, because it may be impossible to differentiate between multicystic kidney and Wilms' tumour. Even when the cystic mass is found accidentally without any referable symptoms, nephrectomy is indicated, for malignant degeneration of the multicystic kidney has been reported (Gütter & Hermanek 1957). Before operation the condition of the opposite kidney should be examined.

The operation was performed in 6 of our cases (Cases 5, 8, 11, 14, 15 and 16). Postoperatively, 2 newborn infants died, one of sepsis (Case 8), and the other of complications mainly due to oesophageal atresia treated operatively 8 days previously (Case 16). The 4 surviving patients have done well since their recovery from the laparotomy, although one of them (Case 11) has marked hydronephrosis on the contralateral side.

The prognosis is said to be good if the function of the contralateral kidney is normal (Menashe & Smith; Weinberg *et al.*). However, of the 19 infants of our series only 4 survived; the contralateral kidney was anomalous in 7 cases, and normal in 12. The high mortality is strongly contributed by the other congenital anomalies, which were found outside the urinary system in 9 cases. Of the non-operated 13 cases, anomaly of the opposite kidney is considered to have been the cause of death in 4 cases (Cases 6, 7, 10 and 18); in 4 cases the infant died of associated malformations outside the urinary tract (Cases 2, 4, 12 and 13); 5 patients died of unassosiated diseases: hyaline membrane disease (Cases 3 and 19), foetal erythroblastosis (Case 17), prematurity and syphilitic cirrhosis of the liver (Case 9), and gastroenteritis (Case 1). Of the 5 patients in whom the multicystic kidney was the only malformation found, 4 died (Cases 1, 3, 8 and 9) but in none of them was the cause of death directly referable to the urinary organs.

The frequent occurrence of associated congenital anomalies greatly impaires the statistical prognosis of the disease. Where the unilateral multicystic dysplasia of the kidney is the only lesion found, the prognosis will be good after successful removal of the cystic mass.

Symptoms and Signs

Multicystic dysplasia of the kidney may be so massive as to obstruct the delivery of the child (Gayet & Leclerc 1957). In the majority of cases no symptoms referable to the urinary tract have been present (Abeshouse), and the multicystic mass may not produce any symptoms until found accidentally in connection with an other examination. In the newborn period a palpable mass in the loin has been the only sign in most instances (Spence *et al.*). Sometimes by compression the cystic tumour has caused symptoms of intestinal obstruction (Froboese; Weinberg *et al.*). In a few cases dull pain in the loin, fever, malaise, urinary infection or hypertension have been noted (Abeshouse). In most of our cases the multicystic dysplasia of the kidney was a secondary finding at autopsy on infants dying of other congenital anomalies or of unassociated diseases. In other cases a palpable mass was the main cause for admission. Case 16 showed symptoms of intestinal obstruction after operation for oesophageal atresia.

The diagnosis cannot be made with certainty until the cystic kidney has been removed. A palpable lobulated tumour is very suggestive of this diagnosis. The multicystic kidney may be revealed by transillumination (Weinberg *et al.*). The majority of cases in which excretory urography was performed showed no function on the affected side (Menashe & Smith). In a few cases reduced renal function was observed, but the pathological finding was typical also in these instances (Menashe & Smith). In none of our cases in which urography was performed, was demonstrable excretion noticed. Usually the non-functioning kidney is presumptive of diagnosis (Lauret). In roentgen examination the colon may be dislocated forwards. At cystoscopy the diminutive or absent ureteral orifice may be observed (Williams). When ureteral catheterisation has been successful, a rudimentary renal pelvis or atretic ureter may be visualized.

In the differential diagnosis, Wilms' tumour, neuroblastoma, hydronephrosis, true polycystic kidney and other intra-abdominal tumours should be taken into account. In our cases the diagnosis was suggested by palpation in 6 cases. Urography was suggestive in showing non-functioning kidney. Usually the preoperative diagnosis was Wilms' tumour.

and 3 patients had anomalies in and outside the urinary organs. The most common concurrent malformation was oesophageal atresia being present in 5 cases.

After a short embryological review the theories of cystic disorders of the kidney presented in the literature are mentioned. In a discussion of the origin of multicystic dysplasia of the kidney, the significance of the ureter and hilar vessels, the location of the cystic mass, associated anomalies, dysplastic elements and the function of the multicystic kidney are discussed in detail. A probable metanephric origin is suggested by a normal ureter and normal hilar vessels, whereas a mesonephric origin is suggested by attachment of the testis and epididymis to the cystic mass and absence of the ureter. The macroscopic and microscopic structure was nevertheless similar in all cases.

The anomaly is thought to be due to an early disturbance in the development of renal blastema, which prevents the union of the uriniferous tubuli with collecting tubuli (the theory of Hildebrandt).

An etiological nomenclature and classification for certain cystic disorders of the kidney is presented. All the cystic kidneys, which microscopically contain primitive dysplastic elements, should be classified as kidney dysplasias. Baggenstoss has suggested the term dysplasia to reveal the presence of primitive elements foreign to the normal kidney. The subordinate grouping is suggested by the macroscopic appearance of the lesion. This subgrouping also roughly describes the severity of the lesion.

1) Focal cystic dysplasia (solitary or simple renal cysts); otherwise normal kidney with normal function.

2) »Multilocular cystic dysplasia»; one part of the kidney involved, function somewhat impaired.

3) Multicystic dysplasia; the whole kidney replaced by primitive connective tissue and cysts, no normal functional parenchyma.

In so far as the so-called (bilateral) polycystic kidneys contain dysplastic structures, they also should, in our opinion, be classed under kidney dysplasias.

Any combination of these typical gross appearances is possible.

The preliminary diagnosis of multicystic dysplasia of the kidney is usually made by detection of a palpable mass. Symptoms are mostly due to compression of the adjacent organs. Nephrectomy is the only treatment possible provided the function of the contralateral kidney is assured. Malignancy cannot be excluded without operation. The prognosis in the newborn period is greatly obscured by a large number of associated anomalies.

Summary and Conclusions

From the Pediatric Department of the University Central Hospital 19 cases of congenital multicystic dysplasia of the kidney are reported. No report based on the observation of so many cases has previously appeared. The age of the patients at the time of autopsy or of operation varied from 1 hour to 1 year 8 months. In 15 patients autopsy was performed and in all except 2 microscopic examination of the diseased organ was carried out. In the remaining 4 cases, the operative specimen was examined microscopically.

The incidence of congenital multicystic dysplasia of the kidney was 0.05% of pediatric hospital admissions and 0.5% of pediatric autopsies performed during the 12 years period. The last 12 cases were found during the last 3 years and from this time the incidence was 0.085% of admissions and 1.3% of autopsies. The figures are much higher than would be expected from the rather scanty reports.

There were 17 unilateral and 2 bilateral cases. In one of the bilateral cases the multicystic structure was limited to one part of the kidney. The number of gross cysts varied between 2 and 20. In 18 cases the cystic structure was situated in the normal kidney area, in one it was ectopically at the pelvic brim. The ureter was fairly normal in 8 cases, rudimentary or atretic in 7 cases. In one case the ureter was totally absent. The hilar vessels were normal in 3 cases and anomalous in 2 cases; in the others no record of the state of the hilar vessels was available.

A detailed description of the microscopic findings is given. Between the cysts the stroma was composed of primitive connective tissue, in which various primitive dysplastic structures were embedded. In the cyst walls the connective tissue was dense and intermingled with smooth muscle fibres. The cysts were lined with cuboidal to flat epithelium. In some cysts a pseudostratified epithelial lining was seen. Primitive tubuli and glomeruli were seen in all kidneys. A rich capillary network was an equally constant finding. In 9 cases primitive cartilage and in 6 cases lymphoid accumulations were present. Calcifications, often present in adults, were not seen in this material, and they were therefore considered to be secondary changes.

A large number of associated anomalies were present. Only in 5 patients could no associated anomalies be found. In addition to the multicystic kidney, 4 patients had other anomalies in the urinary system, 7 patients had anomalies outside the urogenital tract,

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CLARENCE·CRAFOORD

Clarence Crafoord was born on May 28, 1899, and seventeen years later he had already embarked upon his career as the infant prodigy—and the "enfant terrible"—of Swedish surgery. A few years later and the roads between the Anatomy Department at Norr Mälarstrand and Mörby Hospital were being

for without heparin, its most important instrument, the heart-lung machine, could not be used.

K. H. Giertz was right—Crafoord was a hospital cat or, more precisely, a Sabbatsberg cat. He was, like the cat, faithful to the house. What was to be Europe's first and the world's perhaps most famous thorax clinic grew up at the old hospital. It was, however, still a general surgery department; but Crafoord gradually went over entirely to thorax work, while that which in the Sabbatsberg terminology was referred to as "the small surgery"—i.e. ventricular resections, nephrectomies, colon resections, rectum amputations etc.—was managed by his co-workers.

In the subsequent years a pioneering achievement that will go down in surgical history was carried out within the walls of the old and unmodern hospital. When as the first in the world Crafoord operated on coarctation of the aorta he confirmed once more his position as the foremost name in thoracic surgery. "He has the ball" was how the situation was described by an American thorax surgeon. In the long Sabbatsberg corridors and swarming round the operating table one found a numerous and extremely cosmopolitan crowd of various hues, eagerly gesticulating and talking in many tongues. Did this disturb the work? Scarcely! Clarence was like a fish in the water in this milieu.

The next development was the modern clinic for thoracic surgery at Karolinska Sjukhuset. It has grown up, so to speak, as Clarence Crafoord's panoply. It is a part of him, just as the claws, the teeth and the mane are part of the lion. Indeed, it is the Crafoord Clinic.

Sixty years is no great age against the background of this great life's work. And it should be noted that this achievement has by no means always been a matter of fair weather sailing. He has had many contrary winds to contend with, not least in the form of three protracted periods of serious illness, that might have broken down and defeated a less dynamic person lacking Crafoord's devotion to his work. As a matter of fact, he has gone forward with something of the irresistible momentum of a force of Nature.

Clarence Crafoord is now celebrating his sixtieth birthday. It is hard to grasp that so many years have passed since the lanky, long-haired youth, third assistant surgeon at Mörby, stood up and communicated his two cases of embolectomy. But in the course of these years an important chapter in surgical history has been written, in which Crafoord is the main actor. He has in an unique way created an international reputation and respect for Swedish surgery. The "enfant terrible" of Swedish surgery has become the grand old man of world surgery, around whom surgeons from all over the world and innumerable patients from many countries are now assembled to pay devoted and grateful homage.

Ivar Palmer

rendered unsafe by a lanky, long-haired and long-nosed youth, who drove at a tearing speed between these two institutions on a motor-bike, thus combining a post as clerical assistant at the one place with a permanent appointment as third assistant surgeon at the other. He went his own way and was an advanced surgeon before his comrades had collected their wits to do more than stare in amazement.

When, as the youngest assistant surgeon at his hospital, he stood up in the Swedish Surgical Society and gave an account of two operated and surviving cases of embolectomy in the pulmonary artery, his name went out over the world. But the old heads of the clinics shook their heads dubiously and muttered to themselves. An "enfant terrible" of surgery.

It frequently happens to us doctors that medical experiences in youth determine our future field of work. That these two remarkable cases helped to guide Clarence Crafoord's footsteps to the thorny pioneer path of thoracic surgery is surely beyond doubt. But another very important contributory factor was certainly the collaboration with his first and last and, on the whole, only chief, K. H. Giertz, enthusiastically interested in thoracic surgery, dynamic and broad-minded as a man, as a researcher, and as a surgeon. K. H. Giertz was thoracic surgery's first swallow in the North; it fell to Crafoord's lot to carry on the work. They worked together for a very long period, nearly twenty years, and the relationship that developed between them is best characterized by the word symbiosis. They were dependent on each other, though in different ways, and they found strength with each other. A finer relationship between assistant and chief cannot be imagined.

This is true even if it naturally often happened that K. H. protested. Anything else would be inconceivable with such an intense assistant. "Say, which of us two is supposed to be operating?" one might hear when standing behind one of them as a "strap-hanger". And when one went the rounds with K. H. during Crafoord's holidays, when there would be, as it were, a breathing space in the department, one might, in spite of holidays, see a well-known figure descending the stairs—two or three at a time—to department 6C underground, where the thorax cases were placed, while K. H. would snort impatiently: "Crafoord is certainly a proper hospital cat!"

It was during those years that with his usual intensity he occupied himself with the task of trying out heparin as a prophylactic against thrombosis. This broadly planned investigation implied an added burden of work and entailed all sorts of vexations for all of us. I remember from this period an occasion when I was struggling with a prostatectomy that was bleeding unpleasantly and unwontedly. Crafoord was standing at the door of the operating theatre and looking interested. I was seized with a horrible thought: "Don't say you've given him heparin?" — "I have; but that's not why he's bleeding!" was the consoling reply. His interest in heparin strikes one now as almost visionary, when one thinks of the role this drug was destined to play in modern heart surgery;

the main reason why so far surgeons have not ventured, with the certainty of success, into the cavity of the chest, has been the direct risks to life, which have been associated with such a procedure.

If we study the history of our attempts to overcome the dangers of operative pneumothorax, we become aware of a peculiar circumstance; that only very recently have surgeons developed the method which physiologists, in their experiments with animals, have made use of for centuries. Moreover, in my experiments with animals, this method has been found to be absolutely reliable.

The method consists in a tube hermetically bound into the trachea, after which air is rhythmically blown into the lungs with a bellows.

This technique has been used in both France and America; but for different reasons, some of which are quite incomprehensible in so far as human beings are concerned, it has come into disrepute.

Without detaining you by going into the historic and evolutionary phases of the question, I will simply mention the fact that artificial respiration for the relief of asphyxia due to suffocation and drowning had already acquired a remarkable degree of development as early as 1892, when various pumps and bellows for simple insufflation and for combined insufflation and aspiration of the lungs had been devised by several ingenious experimenters. The practice of artificial respiration by mechanical aids suffered a decisive setback, however, as a result of the exhaustive experimental research undertaken by le Roy d'Etoiles in 1829. The French Academy appointed a special committee, which confirmed le Roy's observations. These observations showed that the sudden, violent injection of air into the lungs often caused acute emphysema, rupture of the smaller bronchi and laceration of the lungs. After this discouraging report, nothing was done to advance the practice of artificial respiration by mechanic aids until 1845, when a new movement was started by Chaussieur and Depaul, who were professors of obstetrics at the Faculté in Paris. But artificial respiration by intralaryngeal intubation and insufflation was relegated almost exclusively to the accoucheur; and nothing was done to promote its application to the emergencies arising in surgery, until 1897–98, when the rapid development of surgery aroused a new interest in, and created a demand for, a reliable means of counteracting the danger of asphyxia and pneumothorax. At that period, Quenu and Longuet, Tuffier and Hallion, Doyen and possibly Pean, in France, and Milton in Egypt, had realized the possibilities of mechanic insufflation, and had made notable experimental and clinical contributions to this technique. But, before Sauerbruch, with the exception of Doyen's apparatus, no simple and reliable appliance for the practice of artificial respiration had been devised or put to the test of clinical experience in Europe. In 1897 Dr. Northrup, of the Presbyterian Hospital of New York, demonstrated the value of the ingenious Fell O'Dwyer apparatus as an aid to artificial respiration in the treatment of opium narcosis and other non-surgical conditions. In 1898 Dr. Parham of New Orleans used this ap-

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The Development of Respiratory Apparatus for Thoracic Surgery[1]

† K. H. GIERTZ

On one occasion during his last years and before he was stricken with brain embolism, K. G. Lennander, who was my teacher, said to a few of us, his youngest pupils, "How you boys are to be envied, you who will live to see so many new surgical victories, which I shall never see; victories of which we are at present unable even to dream". At that time it seemed to me scarcely credible that his prediction would come true—for not only did I regard this remarkably intelligent and skilful man with such admiration that, without further ado, I dismissed the possibility of anyone being able to surpass him, but I also underestimated his great capacity to see into the future. For, in many respects, he was before his time and foresaw both in which branches of medicine, and in what parts of the world, development would be most rapid. I recollect how in 1904 he pointed out America as the country with which we should try to get into touch intellectually, more than we had done previously.

[1] From an unpublished, posthumous manuscript written in 1935. From 1928 to 1942, the author was Surgeon-in-chief of Sabbatsbergs Sjukhus, Stockholm.

At the time of Lennander's death, intrathoracic surgery, among other forms of surgery, was not on a very high level, and was chiefly confined to incisions of empyema and to abscesses of the lungs. Some solitary cases of successful operations of both the heart and lungs were certainly known through casuistic items of information; but on the whole, operations of the organs inside the cavity of the chest were terra incognita; furthermore, they were feared on account of the direct risk to life connected with the operation.

In spite of the progress made during recent years, an operation upon organs located in the chest cavity is still rather rare; and it will probably be quite a long time before the surgeon will attack organs, situated in this cavity, with the same sureness and persistence as he deals with organs in the other cavities of the body. To a great extent, this is due to the fact that diseases of the organs in the cavity of the chest have not been found to respond so readily to surgical treatment as diseases, for example, in the peritoneal cavity, where, with the aid of antiseptics and anesthesia, we have gained such great victories. But

provide more space for manipulation. The wall was made partly of balloon cloth, to enable the anesthetist to make himself heard.

The most luxurious low-pressure chamber that has been constructed was most probably that used by Willy Meyer in New York. At a very great sacrifice to himself, Meyer fitted up a separate department for intrathoracic surgery, with a universally differential chamber in which he was able to make use of high or low pressure at will.

Brauer's high-pressure box was a great advance. Here, the patient's body lay free, and the operator and assistants were able to remain in an ordinary operating theatre. Only the patient's head and the arms of the anesthetist were enclosed in the box where the air was compressed. Experience proved that, in spite of all Sauerbruch's theoretical objections to the high-pressure process, it could function just as satisfactorily as the low-pressure method. Many different kinds of high-pressure apparatus were now introduced. In some of these, e.g. in Engelken's apparatus, the anesthetist is placed in the high-pressure box. The technique was considerably improved when Tiegel showed that Sauerbruch's process could be just as readily applied by placing an airtight mask over the patient's mouth and nose. The patient was allowed to breathe, through a mask, air or oxygen under increased pressure. A large number of such apparatus were now designed and made; the best known of which in Europe are probably those devised by Tiegel, Lotsch and Mollegaard.

In 1908 Samuel Robertson of the Harvard Medical School used a positive pressure apparatus with a mask for operations on dogs.

In spite of the greater convenience and ease in handling the high-pressure apparatus, and although experience showed that they were practicable, the old, debated question of the physiological superiority of low or high pressure remained unsolved.

The researches conducted by various investigators seemed to indicate the absolute superiority of low pressure. Consequently, after visiting the foremost clinics in Germany and Switzerland where lung surgery was practised, in 1912 I constructed for my hospital a low-pressure chamber, making use of the mask type. In this way I obviated all the disadvantages and drawbacks attaching to Sauerbruch's method, where ventilation is far from ideal, and the difference between high and low pressure must be nil.

In 1910 Meltzer and Auer reported a new ventilation method from America, which, according to the inventors, was based on entirely new principles. An ordinary catheter, 22–24 is inserted into the patient's trachea so far that the point is a few centimeters above the bifurcation of the trachea. The catheter is connected with a blower which forces in air under a pressure exceeding that of the atmosphere by about 24 mm of mercury. In this way, the air that is blown into the trachea turns and passes out at the sides of the catheter. According to the first statements made by Meltzer, the ventilation was so good that respiratory movements would cease. This was not confirmed. The patient still breathes,

paratus with great success in removing a very large tumor of the chest walls. Dr. Rudolf Matas of New Orleans, whose significance for the early development of thoracic surgery cannot be too highly estimated, published in 1902 a paper on artificial respiration by direct intralaryngeal intubation with a modified O'Dwyer tube and a new graduated air pump, in its application to medical and surgical practice. He had no opportunity to try the apparatus in operations on human beings.

The entire question of the possibility of operating on the thorax without endangering life was given a fresh impetus by Sauerbruch in 1904. The renowned German surgeon, who is now practising in Berlin, was then a young assistant to the great Miculicz in Breslau. Miculicz was interested in the problem of extirpating tumors of the intrathoracic part of the oesophagus. In order to be able to do so, the problem of sufficient ventilation, in spite of an open pneumothorax, had to be definitely solved; and young Sauerbruch was entrusted with this task.

Sauerbruch started out by trying, during the operation, to restore the physiological difference in both the external and internal pressure on the thorax, which is disturbed by opening the thorax. He endeavoured to accomplish this by constructing a chamber enclosing the thorax of the experimental animal, in which the air pressure was reduced, whereas the head was allowed to breathe air at normal pressure, through an opening in the wall. Vice versa, the head of the animal could be placed in a bonnet, in which the pressure was higher than that of the surrounding atmosphere.

Irrespectively of whether a pneumatic low-pressure chamber or a high-pressure box was used, it was found that the experimental animal was able to breathe spontaneously. By this process the immediate risks to life were obviated, and operations within the thorax could be performed calmly and without giving rise to anxiety. Sauerbruch considered, in the light of his studies and experiments, that the low-pressure process was the more important physiologically and could be applied without danger. Consequently, he designed a large pneumatic chamber, which was installed at the Breslau Surgical Clinic. The patient lay inside the chamber with his head protruding through an opening in the wall. A rubber neck-cuff was placed around the patient's neck to secure airtightness. The operator, assistants, and nurses were inside the chamber, where the air was rarefied by means of an electric fan or pump. But such a chamber entails considerable drawbacks and disadvantages. The patient is attached to the wall by the neck-cuff or collar, and is difficult to move during the operation. The free space available for the operator and assistants is restricted; the heat in the operating chamber is considerable, and the operator and the anesthetist are separated by a wall and find it difficult to make themselves mutually understood.

Sauerbruch simplified his chamber so that it could be transported. The opening for the neck could be made to vary for different heights. The wall nearest to the patient's head was prolonged so as to

sure should be performed with the utmost care when both pleural cavities have to be opened. When differential pressure is used, it should be carefully observed that the other pleural cavity is not opened.

Just as strict a warning must be entered against the statements by otherwise competent lung operators, that, on the whole, arrangements for ventilation need not be made in intrathoracic operations.

Because of lowered ventilation, even with proper handling, and of quite insufficient ventilation, resulting from wrong handling, there is a danger in differential-pressure respiration, which makes it necessary, on the slightest suspicion of lack of ventilation, to adopt —in prolonged operations possibly to resort to—prophylactic measures. This is done by closing the thorax by oxygen respiration and intermittent superpressure respiration which is easily established by the rhythmic removal of the mask. With an adequate knowledge of its deficiencies and of the means to be adopted against these dangers, it is, nevertheless, possible in pleurotomies to make use of the differential-pressure process.

There is still another drawback or disadvantage—the detrimental effect on the minor circulation. With a closed thorax, a rising superpressure causes a rising intrathoracic pressure, which leads to a compression of the capillaries of the lung, with ensuing increased pressure in the right ventricle or pulmonary artery respectively, a diminished current speed through the pulmonary vessels and a lowered aorta pressure. The increased intrathoracic pressure impedes "the physiological suction" of blood from the periphery to the right ventricle of the heart, and constitutes an obstacle to the diastole of the heart.

With high degrees of differential pressure and a closed thorax, these phenomena are a real danger, at least for a weak heart. With low degrees of differential pressure, they are, according to my experience, not dangerous.

Since, by animal experiments, I had learned to understand the insufficiency and danger of differential-pressure respiration, I proceeded to try to find a reliable method. The ventilation method which I recommended in 1916 was the old process consisting in the rhythmic injection of air, which had been used by physiologists. Nevertheless, it has been unfairly discredited in respect of operations on animals; and in regard to human beings, it has been applied only by way of exception. However, my experimental operations go to prove that the method is clinically practicable. It provides safe ventilation, and, if methodically and properly used, does not involve any danger.

I used a modified Lotsch superpressure apparatus, in which the air current was interrupted from 8 to 16 times a minute. The volume of compressed air was regulated by a slide-valve. The most important feature of the method is a properly located intrathoracal tube, which must close tightly in the tracheal walls. I obtained a suitable tube of this kind by adjusting a distensible rubber balloon round the laryngeal end of Kuhn's intubarim. By means of prewarmed and water-saturated air injected

although the respiratory movements may be very slight. Moreover, according to Meltzer's first report, there would be no need to interrupt the air current.

The method was widely used in Sweden as a suitable means of producing general anesthesia. Other vapors are infused together with the air; and experience has shown that in this way a calm condition under narcosis is obtained with only a slight consumption of ether; and vomiting or post-operative complications are avoided. But the method involving an open thorax, as first described, has not proved effective, since ventilation is inadequate unless the incoming and outgoing current of air is interrupted, in order to give the lungs time to collapse and to exhaust the air from the lung-alveoli. Finally, as a result of these considerations, the method introduced by Meltzer and Auer is only a modification of physiological, artificial respiration.

It was indubitably Sauerbruch who inspired thoracic surgery with new life, when in 1904 he introduced differential-pressure breathing.

Respiration under differences in pressure, when properly carried out, removes the immediately dangerous pneumothoracic symptoms; but ventilation is only adequate under certain conditions. In many cases ventilation is quite insufficient, and therefore dangerous. The longstanding controversies about the different physiological values of the various differential-pressure methods, may perhaps be regarded as having been settled by my researches in 1914–16. From a physiological viewpoint both processes are satisfactory.

Now that the question may be considered as settled, we need only take into account the practicability of the different apparatus. From this point of view, the high-pressure apparatus are to be preferred. In fact, other apparatus are now hardly used.

But even when using a well-designed and constructed high-pressure apparatus, an operation within the thorax is by no means free from all danger. Thorough familiarity with the physiological changes, which are brought about by the differential-pressure process in respiration and circulation, is required if a high-pressure apparatus is to be used in thoracotomy without any risks being involved.

In differential-pressure breathing, even when the thorax is closed, ventilation is already detrimentally affected. After pleurotomy, ventilation is certainly made possible, but is greatly reduced. In differential-pressure respiration, the lungs follow, as in ordinary respiration, the movements of the thorax. On inspiration the thorax is enlarged and air is forced through the trachea. In open pneumothorax especially, if on one side—or still worse on both sides—there is a wide thoracic defect, so that there is air, to any considerable extent, between the lung and the thorax or the diaphragm respectively, the lung does not follow the thorax, and ventilation is so slight that a direct risk of asphyxia arises. A very serious warning must be uttered against the belief that every danger to life, in bilateral pleurotomy, is eliminated through differential-pressure respiration. I would earnestly advise that operations under differential pres-

intrathoracic work with either unilateral or bilateral open pneumothorax, and without any respiratory labor being required on the patient's part. Furthermore, the length of each inspirator injection and expiratory exit of gas, the length of each interval between these two operations, and also the quantity of gas which is introduced with each injection, are exactly regulated by mechanical means. It is particularly important that the expiration phase is not the oesophagus, larynx, trachea and the bronchi to be operated upon. In those cases where a flow of secretion may be expected from the whole or from parts of the diseased lung, the bronchi, through which the outflow may be expected, are closed with a narrow gauze swab dipped in pantocain and inserted through a bronchoscope. Such shutting-off of a whole or a part of a lung will surely prove of great importance, since the risk of postoperative complications arising from the diseased parts of the lung is reduced to a great extent by the effective prevention of aspiration affecting the sound side during the operation. In uninfected cases, the tube is inserted as soon as the surface anesthesia is complete; and in infected cases, when the bronchial swab is ready. It is important that the surface anesthesia is really so complete that no irritation occurs when the narcosis tube is inserted and the trachea is made airtight by pumping up the rubber bladder. Otherwise the patient is disturbed and does not sleep quietly.

When the spiropulsator is connected to the patient, who has been carefully instructed respecting the way in which the apparatus works, as a rule he settles down almost at once to the automatic changes of pressure, and his own spontaneous breathing ceases. The gas mixture that is employed at present contains 7.5 % of oxygen (O_2) and 92.5 % of nitrous oxide (N_2O). The respiration frequency is 25–35 per minute, and 500 to 600 cc of gas are consumed for each respiration. The gas mixture is warmed to 30° or 35°C, and is saturated with steam before being administered to the patient. Our patients dropped off to sleep immediately after drawing a few breaths. Subsequently, they had no disagreeable memories whatsoever in the form of asphyxia sensations, nausea, etc.

Some patients reached, after a few minutes, an intoxication stage with strained muscles; and their own respiratory movements often counteracted the impulses of the spiropulsator. We were then forced to administer evipan or a little ether, and the supply of oxygen had to be increased. Nevertheless, in the majority of cases we have succeeded in obtaining a non-reflexive, calm narcosis, with reliable, ideal ventilation. It must also be borne in mind that, on the whole, an extremely profound and reliable narcosis is required in intrathoracic operations, where it is of the utmost importance that the patients are so profoundly anesthetized that reflexes are entirely suppressed, which are released especially in dissection around the lung hilus, and which are dangerous for the organs of circulation. There are two disciplines closely allied with surgery, which it is imperative that the chest-surgeon either masters himself, or in respect of which he can depend on the

at the proper pressure by a safety valve, all dangers—formerly believed to be attributable to rhythmic injection—were overcome.

The only drawback connected with this method is the necessity of intubation; this did not present any difficulties however.

The method has two great advantages, which more than compensate for this slight drawback. Even when there is a bilateral open pneumothorax, where, moreover, the two thoracic walls are removed, ventilation is perfectly reliable, and we avoid any injection of air into the stomach, which, as clinical experience with differential pressure and masks has shown, entails a direct danger to life. At that time—it was during the war—the design of the distensible rubber balloon, in which the tube had to be placed, presented insurmountable difficulties; and consequently, the application of the method in the clinic had to be postponed.

In connection with the tests made to perfect a method for the operative removal of oesophageal cancer, in 1931 closer co-operation was initiated between the oto-laryngological department and my surgical department at the Sabbatsberg Hospital. Gunnar Holmgren suggested that Paul Frenckner, and I proposed that Clarence Crafoord, should participate in this co-operation; and the results, of which I shall now give you a brief account, are mainly the outcome of this collaboration. When working on some other project, which led to the development of the very important bronchospirometric method of examination, Paul Frenckner designed a tracheal tube which, when inserted into the trachea or bronchi, can be made airtight. This tube is introduced by the aid of direct tracheoscopy, and can be very simply manipulated by an experienced practitioner. It is owing to Frenckner's energy that thoroughly good rubber has been obtained for the distensible balloon; and the problem of devising a reliable method of ensuring airtightness has been satisfactorily solved. We have gained sufficient experimental and clinical experience to be able to say that his tube functions perfectly; and that without causing any inconvenience, other than a slight hoarseness, it can lie in position for two hours or longer. With this tube and the rhythmic injection of air, we get, in both experiments and operations, a perfectly reliable and quite harmless form of ventilation. Experimentally, animals, with complete division of the frontal thorax, can be kept alive for as long as may be required.

But in collaboration with Anderson, a civil engineer attached to the Aga Experimental Department, Frenckner also solved the problem of producing a highly effective inhalation apparatus, which he called a spiropulsator. This apparatus functions on the same principles as those adopted in all the Aga intermittent lights (for lighthouses) operated by gas, i.e. various valves open and close at different pressures, determined for each valve in the system to which the apparatus is connected. By a simple grid the respective valves are adjusted to the maximal and minimal degree of pressure required. In this way we get a respiration position between two pressures, which is suitable for

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The Surgeon's Cooperation with the Biochemist

Some Aspects of Blood Clotting in Surgery

J. E. JORPES

The surgeon of today, and especially the thoracic surgeon, must be a physiologist as well. He has to take into account the nutritional state of the patient, his protein, electrolyte and water balance; for a thoracic surgeon, the respiratory and circulatory systems are naturally of paramount importance. Nothing, except the introduction of antibiotic drugs, has so much improved the final results of surgery as our increased knowledge of physiology. One of its highly significant fields is that of blood clotting.

The anticoagulant drugs now make it possible to reduce the danger of thrombosis and pulmonary embolism. When heparin became available, efficient systems for extracorporeal blood circulation could be developed, a prerequisite for advanced lung and heart surgery. More often, the surgeon has to deal with the opposite aspect of blood clotting, in the form of bleeding conditions, culminating in situations where even blood transfusions and ordinary hemostatic measures are inadequate, and specific therapy is called for. To overcome these thrombo-embolic and hemorrhagic complications, the surgeon has to cooperate with a coagulationist.

THROMBOSIS AND EMBOLISM

The story of the introduction of anticoagulant therapy in medicine has been told authoritatively by the participants themselves, in a symposium organized by Irving S. Wright, New York, and published in the January 1959 issue of *Circulation*. I can quote some of the statements I then made with respect to Crafoord's role in the pioneer work on heparin.

"Clarence Crafoord, the well-known Swedish thoracic surgeon, had drawn attention to himself already as a young man, by his numerous pulmonary embolectomies, between 20 and 30. What could be more natural in such a case than to approach a biochemist and ask him to prepare in a pure state the heparin of Howell, to be tried as a prophylactic against pulmonary embolism? This was, in fact, what Crafoord did in 1929. Unfortunately, the only answer we could then give him was *non possumus*. Crafoord, at that time working at Mörby County Hospital in the vicinity of Stockholm, used to pay frequent visits to the preclinical institutions of Karolinska Institutet, discussing respiration physiology with Professor Liljestrand and afterwards dropping in at the Chemistry Department in an attempt to convince us of the necessity of making heparin available.

In 1935, we could instead approach him at Sabbatsbergs Sjukhus, and ask him to test our heparin preparations clinically. Crafoord immediately started a series of experiments heparinizing

expert assistance of his colleagues, viz. roentgenology and bronchoscopy. In fact, the development of thoracic surgery is partly due to the astounding progress made in these auxiliary sciences during the last ten or twenty years.

In the great majority of cases, not only does the careful, not to say minute, local diagnosis depend upon X-ray examinations—here, as in other organic investigations, injected contrasting agents are made use of in order to enrich and complete or to supplement the X-ray picture—but often our entire diagnosis is based on the X-ray examination.

Bronchoscopy has assisted us both diagnostically and therapeutically, in ways we could formerly never have dreamed of. Consequently, as a general rule, we have the possibility of making, before the operation, a biopsy-diagnosis, and of carefully deciding the localisation and development of the process. But we must be prepared for the eventuality that all our diagnostic aids may give us incomplete or erroneous information; and hence we may have to resort to our last diagnostic aid, probatory thoracotomy. Today, one might venture to maintain that exploratory thoracotomy is no more dangerous than probatory laparotomy or trepanation.

more per capita than in other countries —blood analyses are practically never made. If bleeding occurs, a blood transfusion or a protamine injection will immediately normalize the situation.

Many a colleague, less familiar with the physiology of blood clotting, is anxious to have the prothrombin time determined before giving heparin as well. He will be still more confused if the blood sample for prothrombin analysis is taken after giving the heparin injection. Fortunately, no substitute has been found for heparin that could replace the natural product, and would give rise to the same chaotic conditions as those now prevailing in the field of antiprothrombinic drugs. Here, many of the mild, short-acting drugs are administered in a way which makes one recall that patients used to recover—and some of them to die—even in the pre-anticoagulant era.

EXTRACORPOREAL CIRCULATION

Experiments with extracorporeal circulation could only be started when heparin became available (Kolff, 1946). Its multiple action as an inhibitor of thromboplastin formation, as well as an antithrombin, makes it an ideal anticoagulant for this purpose. However, during the course of by-pass, a certain amount of heparin diffuses out through the capillaries, and must be replaced at intervals. At the end of operation, when the heparin is to be neutralized by protamine, its concentration in blood must be determined. Fortunately, protamine can easily be purified to such a high degree that it can be given intravenously (Jorpes, Edman & Thaning, 1939).

For quantitative determination of the heparin in this case, a special technique is applied (Blombäck, Blombäck & Wallén, 1955; Blombäck, Blombäck, Olsson, William-Olsson & Senning, 1959). The amount of heparin cofactor in human blood is too low to allow proportionality between heparin content and length of clotting time in the *in vitro* test. The addition of a small amount of ox plasma, rich in cofactor, corrects the deficiency.

FIBRINOGENOLYTIC CONDITIONS

Failing hemostasis is an unpleasant complication, particularly if unexplained. Among the most undesirable postoperative complications are the fibrinogenolytic bleedings unexplained until recently, but now known to be due to an enzymatic breakdown of fibrinogen. Defibrinogenation through massive intravascular clot formation and peripheral embolization has the same effect. The clinical features are fairly well defined, and the diagnosis is established by the laboratory tests.

Here, the surgeon and the biochemist meet again. Thus, one day in the beginning of 1955, Crafoord once more called upon us, this time asking for pure fibrinogen. During a visit to South America in 1954, he had lost a patient in a fibrinolytic crisis, the first case he had ever seen. Strangely enough, soon after his return to Sweden, there occurred an additional three cases, two of which were fatal (Blombäck, Blombäck, Senning & Wallén, 1955). Pure fibrinogen was not available at that time; the costly products obtainable were unstable, relatively

patients postoperatively. Many an older colleague shook his head and expressed his dislike of such experiments, in which the patients were "made hemophiliacs" for a time. Crafoord, anyhow, fulfilled his intentions and heparinized 325 patients postoperatively. His colleague, Per Wetterdal, of the Gynecology Department of the same hospital, contributed with another 231 cases and Leissner of the Maternity Clinic of the University of Lund heparinized 309 patients post partum. In total, about 865 cases were thus heparinized after operation or childbirth. A high frequency of thrombosis, at least 3–4 per cent, and possibly still higher, was expected in Crafoord's series consisting only of patients over 35–40 years of age and with operations known to be followed by a relatively high percentage of thrombo-embolic complications. Practically no incidences of that kind occurred. Although Wetterdal's and Leissner's series comprised only selected cases expected to give a high frequency of thrombo-embolism, no complications were observed during the first 10–15 days after operation or delivery. Among the 657 (325 + 140 + 192) cases receiving 250 mg heparin or more daily for 5–10 days no signs of thrombosis occurred.

Similar experiments were at the same time going on in Toronto, Canada. Gordon Murray at the Toronto General Hospital contributed at first 260 cases and then in total 400 cases treated prophylactically with heparin. He reported results equally as good as the Swedish group."

Crafoord made an essential contribution in another respect as well, namely, by using his influence to get the city authorities of Stockholm to pay our experimental costs. The research funds available were small, allowing annual grants of 500 to 1000 dollars for our work. The total amount of support obtained from research foundations during the years for our work on heparin, leading to elucidation of its chemical nature, to demonstration of its presence in the mast cells and to its introduction in clinical medicine, amounted to 50,000 Sw. crowns (10,000 dollars). At one time, in 1936, one whole year had been lost, and anticoagulant therapy delayed, because of lack of funds. The head of the City Hospitals of Stockholm then supplied us, on Crafoord's recommendation, with 40,000 Sw. crowns in order to keep the work going. He wanted to know whether the new kind of treatment of thrombo-embolic cases with heparin could shorten the stay in hospital from six weeks, as it had been previously, to one week, in which case it would pay to support a research project. He soon got the money back indirectly.

Heparin, like the antiprothrombinic drugs, came to stay. A study of the overwhelming literature in this field reveals, however, that the therapeutic potentialities of heparin have been poorly exploited. There is still much teaching to be done for the instruction of the younger generation of physicians in the proper use of heparin in acute thrombosis, as outlined by Merz (1954, 1955), Bauer (1955) and Zilliacus (1946, 1955). It is not in the interest of the patient to be treated routinely, mild and severe cases alike, with inadequate preparations under poor control of the prothrombin level. Only adequate heparin therapy can cut off an acute thrombo-embolic complication efficiently, and in long-term anticoagulant therapy a poorly controlled prothrombin level is essentially dangerous. All these considerations make a coagulationist obligatory in every large hospital unit. The use of heparin is unnecessarily complicated by the demand that heparin therapy should be carried out under continuous control of the coagulation time. In fact, in Scandinavia —where heparin is used several times

either with fresh plasma or with the plasma fraction containing antihemophilic globulin.

Hemophilia A.—There is by now quite considerable experience in this country of the treatment of hemophilia A cases with the I-0 plasma fraction of Blombäck & Blombäck (1956), prepared in our laboratory at Karolinska Institutet. Altogether 22 patients have been treated on a total of 140 occasions, and 9 patients with v. Willebrand's disease on totally 45 occasions (Nilsson, Blombäck & Blombäck, 1959). Puncture of joint bleedings, tooth extractions, an appendectomy, an ileus operation and a nephrolithiasis operation have been performed on the hemophiliacs, and hysterectomy on a patient with v. Willebrand's disease. As a rule, the preparations have been given on vital indications to patients bleeding excessively. On no occasion did the treatment fail, no side reactions occurred, and no resistance to the AHG developed, not even in patients treated up to 20 times in the course of 2 years.

The I-0 fraction of Blombäck & Blombäck can be stored as the lyophilized product. Its antihemophilic activity is titrated against a standard sample of fraction I-0, using hemophilia A plasma as substrate (Nilsson, Blombäck & v. Francken, 1957; Blombäck, M., 1958). A scheme of administration has been elaborated which, in most cases, seems to ensure normal conditions for operation.

In the course of this work, some experience was gained of the properties of the hemophilia A factor or factor VIII. It is known to be consumed with extreme rapidity during the first phase of coagulation, partly during thromboplastin formation and very quickly through the action of thrombin. Definite precautions must therefore be taken in sampling of the blood and separation of the plasma. In most of the severe cases treated successfully with the I-0 fraction, attempts had earlier been made to correct the bleeding by administration of fresh blood or plasma, but without success.

This finding actualizes a discussion regarding the fate of antihemophilic globulin, factor VIII, in the course of extracorporeal circulation. The excessive surface contact offers great possibilities for thromboplastin and thrombin formation. It therefore seems reasonable to believe that, during by-pass, factor VIII will be destroyed to a considerable extent. In Crafoord's clinic, fraction I-0, containing AHG, has in fact been given in several cases at the end of a lengthy operation, when other measures failed to arrest the bleeding. In a number of them the effect was almost instantaneous, giving the impression that the fraction exerted a specific action.

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insoluble and contained 50 % impurities, causing side reactions. Pure fibrinogen was needed in our laboratory as well, to be used as substrate for work on the heparin cofactor of plasma. Consequently, new efforts had to be made to obtain pure fibrinogen in large quantities. They resulted already in the same year in plasma fraction I-0 of Blombäck & Blombäck (1956), a 90 % pure, stable fibrinogen, giving no side reactions, and containing both the antihemophilic globulin A and the factor lacking in v. Willebrand's disease. This new technique for preparation of pure fibrinogen, free from prothrombin, was soon adopted by pharmaceutical houses, which made the product—although still expensive—nevertheless available on a large scale.

HEMORRHAGIC DIATHESIS AND HEMOPHILIA-LIKE CONDITIONS

Severe hemophilia and thrombocytopenia will be detected in the preoperative routine blood analyses, and may form a contraindication to operation. Mild cases are, however, apt to be overlooked. This also applies to patients with *v. Willebrand's disease.*

Recent work performed in Sweden has called renewed attention to this disease (Nilsson, 1957; Nilsson, Blombäck & v. Francken, 1957; Nilsson, Blombäck, Blombäck, Jorpes & Johansson, 1957; Jorpes, 1959; Nilsson, Blombäck & Blombäck, 1959). No less than 20 families with this autosomal, dominant hemorrhagic diathesis, affecting both sexes equally, have been detected within a few years in Sweden. The families are large, and the disease is evidently more common than hemophilia A and B together. The individual family members are usually ignorant of their disease, at any rate of its seriousness. Only a few members of the families, men and women alike, are real bleeders. There is not only a tendency to capillary bleedings, but also a reduction in the plasma content of antihemophilic globulin (AHG), which parallels the severity of the symptoms, and in severe cases falls to as low as 5 % of normal or less.

The cases with 30–60 % of antihemophilic globulin deserve special attention. In situations where there is an acute, large consumption of AHG through over-production of thromboplastin and thrombin, e.g. in connexion with operation, tooth extraction or traumatization, a temporary AHG deficiency may develop, and can become fatal. In analyzing 13 patients and 93 of their relatives, Nilsson, Blombäck & v. Francken (1957) found that the 13 patients and 4 of their relatives had values below or around 20 % of normal. Of the siblings on the side from which the disease came, 27, or 29 %, had AHG values between 30 and 60 %, which is regarded as below the normal limit. This implies that, in addition to the bleeders, a considerable number of their siblings in the family branch carrying v. Willebrand's disease have a subnormal plasma content of antihemophilic globulin.

These persons, who are latent bleeders, can cause the physician and the dentist serious trouble until their disease is duly recognized. Once the diagnosis is established, the patients can be treated prophylactically and therapeutically in the same way as the hemophilia A cases,

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Pulmonary Ventilation during Thoracic Surgery

With Special Reference to the Use of the Engström Respirator and a Ventilation Nomogram

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The maintenance of adequate alveolar ventilation during thoracotomy is connected with great difficulties on account of the changes arising in the mechanical conditions which constitute the necessary basis for normal respiratory work and a normal gas exchange in the lungs. These difficulties have led to the construction of various technical devices to support the ventilation in connection with unilateral or bilateral thoracotomy. Thus pressure differential respiration was introduced by Sauerbruch in 1904. This method was made the object of strong and justified criticism by Giertz in 1916, who also indicated a better method, the so-called rhythmic air-insufflation, which was later modified by Freckner, Andersson & Crafoord in 1938, when the so-called spiropulsator was constructed and tried out. This apparatus has implied a very great advance in thoracic anesthesia and has helped to reduce the risk of hypoventilation in thoracic operations. It is, however, difficult to know exactly what ventilation is supplied to the patient with this apparatus, and its functioning is dependent, moreover, on the efficiency of the carbon dioxide filter used. Thus when in 1953 Engström's volume-cycled respirator proved suitable for anesthesia inasmuch as it permits of exact control of the ventilation volumes applied, and functions, furthermore, in a so-called half-open system, i.e. without carbon dioxide filter, it seemed to us to be of interest to find out what amounts of ventilation are required for the maintenance of adequate alveolar ventilation in connection with different forms of thoracic operation when this respirator is used. As far as we are aware, no such study has previously been made, apart from certain observations in connection with extracorporeal circulation (Norlander, Pitzele, Edling, Norberg, Crafoord & Senning, 1958).

MATERIAL

Altogether 13 patients were examined. These were divided into two groups, according to the nature of the surgical operations performed. In the one group, consisting of 6 patients, the surgical operations were carried out on the lungs,

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TABLE 2.

Case no.	Max. breathing capacity	Resid. vol./ total lung capacity %	Vital capacity (l)
1	55	58	2.23
2	73	45	2.81
3	48	41	3.27
4	78	39	3.60
5	92	42	2.57
6	84	43	2.84
7	55	—	2.00

which were the seat of pathological changes that had preoperatively given clinical signs of impaired lung functions. The other group comprised 7 patients who were all operated upon for the correction of cardiac or vascular changes, but in whom there were no primary lung changes with the exception of two cases. The composition of the material, the vital statistics and other data are given in Tables 1 and 2.

METHODS

Anesthesia

The patients were given premedication in the form of morphine-scopolamine and a barbiturate per os. Anesthesia was induced with pentothal. After the admixture of oxygen and nitrous oxide intubation was performed in succenylcholine apnea. After a period of spontaneous respiration for 10–20 minutes in the course of which the patient was placed in the operating position, which was in all cases either left or right thoracotomy position, the patient was connected up with the Engström respirator after previous total muscle relaxation with *d*-tubocurarine. Anesthesia was maintained with oxygen + nitrous oxide in the proportions 1:2 or 1:1, supplemented with small intermittent doses of pentothal or with pethidine. The respirator was from the outset adjusted to a minute ventilation calculated from a ventilation nomogram and then maintained and carefully and repeatedly checked during the anesthesia.

Calculation of the ventilation

Engström & Herzog (1959) have worked out a ventilation nomogram for the Engström respirator (Fig. 1). The nomogram is based upon oxygen consumption and the production of carbon dioxide in basic conditions and R.Q. = 0.8, the dead space of the apparatus and the dead space in the connecting tubes to the patient. Another factor that is taken into account is the "mechanical dead space", i.e. the volume which at every insufflation is compressed in the respirator system and which on exhalation is read off on the gasometer without having been made available for the patient. The ventilation calculated from the nomogram was read off in all cases except case no. 8, a 2-year-old boy; here the ventilation was calculated according to an empiric nomogram for small children based on the same variables as the nomogram for adults and children over 6 years of age.

The respiratory frequency has been 18 or 20 per minute. Where there was a change in the frequency during the operation the supplied volumes were corrected for the change arising in this connection in the dead-space ventilation. Before the pleura was opened a negative

TABLE 1.

Case no.	1. Age & Sex 2. Height (cm) & Weight (kg) 3. Surface (sq.m.)	Diagnosis	Operation	Duration of operation (hrs.)[a]	Duration of anesthesia (hrs.)[a]	Ventilation (l/min.) Acc. to nomogram	Ventilation (l/min.) Given	Frequency of respiration strokes/min.
1.	52, F 165, 57.4 1.65	Empyema after left pneumonectomy	Res. of empyema sac. + thoracic wall trachectom + respirat.	4.10	4.40	7.1	7.1	18
2.	74, M 176.0, 56.5 1.7	Carcinoma with atelectasis of left upper lobe	Left sup. lobect.	1.20	1.50	7.1	7.8	20
3.	60, M 170, 63.8 1.75	Carcinoma of right lung	Pneumonectomy	2.25	2.55	7.9	8.0	20
4.	40, M 172, 72.9 1.86	Bronchiect. of left infer. & lingula lobe	Resect. of basal segm. and lingula lobe left lung	3.20	3.55	8.2	8.0	18
5.	56, M 173.3, 80.6 1.92	Carcinoma of left lung	Pneumonectomy	2.30	3.5	8.0	8.0	20
6.	58, M 167, 69.5 1.78	Carcinoma of left lung	Pneumonectomy	2.25	3	8.4	8.4	20
7.	46, M 172, 72.7 1.86	Constrictive pericarditis	Decortication of pericardium	3.35	3.50	8.4	8.4	18
8.	2, M 87, 9.3 0.48	Patent ductus arteriosus	Division + suture	1.30	3	Ca. 5	5.0	22
9.	43, F 158, 49.7 1.5	Stenosis mitralis	Commissurotomy	2.10	2.35	7.0	7.5	20
10.	49, F 167, 71.2 1.8	Stenosis mitralis	Commissurotomy ad mod. Dubost	1.30	2	7.7	8.0	18
11.	26, F 167, 53.5 1.6	Stenosis mitralis	Commissurotomy	0.45	1.5	7.1	7.0	18
12.	30, F 167.5, 56.2 1.64	Stenosis mitralis	Commissurotomy	1.5	1.40	7.2	7.5	18[b]
13.	26, M 169, 60.7 1.72	Patent ductus arteriosus	Division + suture	2.25	2.55	8.0	8.0	18

[a] Decimals indicate minutes.

[b] Cardiac arrest in connection with the commissurotomy. After heart massage for 1 min. spontaneous rhythm. Postop. no complications.

strain-gauge and a recording instrument. *pH* was determined at 38°C with a glass electrode and a potentiometric pH-meter (Radiometer PHM 22) with phosphate buffers as standard. $PaCO_2$ was determined on whole blood with the method described in 1956 by Astrup. Correction for hemoblogin concentration was applied in accordance with the method described by Norlander, Pitzele, Edling, Norberg, Crafoord & Senning (1958).

Standard bicarbonate was likewise determined according to Astrup 1956. The blood samples were taken in glass syringes previously wetted with heparin and the analysis was performed immediately after the taking of the samples. No double determinations were made. The magnitude of the error due to the method in determinations of $PaCO_2$ with this method is approx. ± 2 mm Hg for a single determination.

The arterial oxygen saturation was determined according to Brinkman & Zijlstra (1949) with a cuvette oximeter (Kipp & Zn, Delft).

The blood samples were taken *before the induction* of anesthesia but after the premedication, and also during the anesthesia, at intervals when a respiratory steady-state was considered to be present.

RESULTS

The analytic results obtained may be seen in Table 3 and in Figs. 2 and 3.

$PaCO_2$

Preoperatively $PaCO_2$ remained within limits which may be considered normal. The mean value for 12 cases was 40.3 ± 1.4 mm Hg. Certain individual variations did, however, occur, as for example in case no. 1, where $PaCO_2$ amounted to 48 mm Hg. During respirator-anesthesia the carbon dioxide tension remained at or below normal values in all cases except two. In these cases, no. 5 and no. 6 (see Fig. 2), the values for the carbon dioxide tension obtained were, with the ventilation administered, 49.5 mm Hg and 48.0 mm Hg respectively. In these cases the ventilation was thus somewhat below par, and in case no. 5 the latter was accordingly increased from 8 to 10 l/min., after which a normal $PaCO_2$ value was obtained. In case no. 6 the ventilation administered was retained and at the time when the next test was made $PaCO_2$ was 47 mm Hg; i.e. practically the same as before. There were no clinical signs of carbon dioxide retention. This patient had signs of shunt mechanism in the lungs with admixture of mixed venous blood to the peripheral circulation, as the oxygen

TABLE 3. Mean value $\pm$ standard error of the mean for pH, arterial carbon dioxide tension and standard bicarbonate before and during anesthesia with mechanical ventilation with the Engström respirator.

	pH	Stand. bicarb., mEq/l	$PaCO_2$ mm Hg
Before anesthesia, $n = 12$	7.41 $\pm$0.02	24.2 $\pm$0,9	40.3 $\pm$1.4
0–60 min. during artif. resp., $n = 13$	7.36 $\pm$0.02	22.0 $\pm$0.7	42.1 $\pm$1.1
90–120 min. during artif. resp., $n = 10$	7.35 $\pm$0.02	21.5 $\pm$0.8	40.7 $\pm$1.5

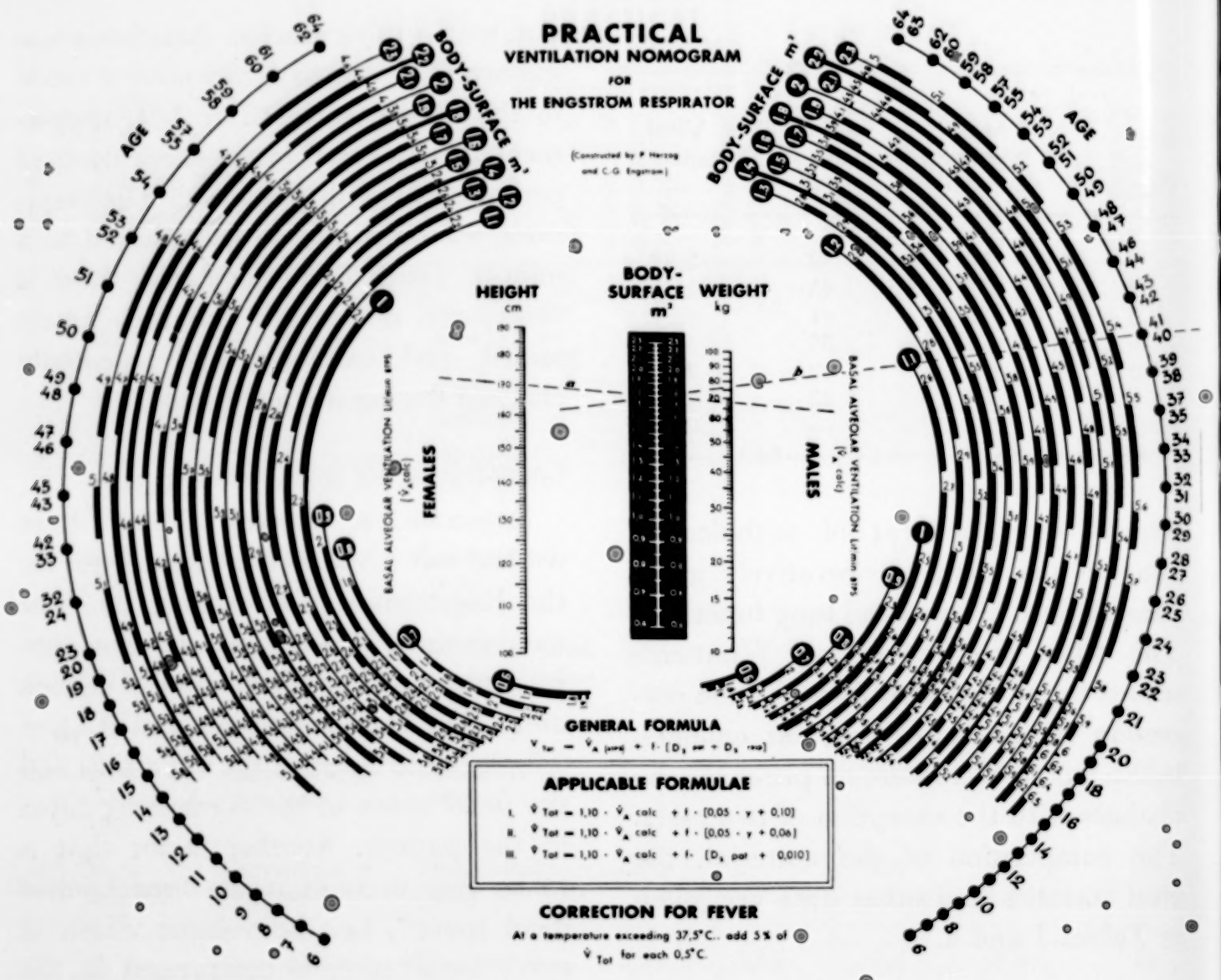


FIG. 1. The ventilation nomogram used for determination of the ventilation during anesthesia.

pressure of −4 to −6 cm was applied during the exhalation. When the pleura was open the negative pressure was removed to prevent an all too strong collapse of the lung, which would otherwise occur owing to the low exhalation resistance of the respirator. In the majority of cases even a slight exhalatory resistance of about one cm was applied, in order to maintain the lungs in a suitable middle position. The minute ventilations applied are shown in Table 1. The volumes administered were checked by reading the values on the gasometer of the respirator. The accuracy for the administered volumes has been estimated as ±0.1 l/min.

Determination of pH, $PaCO_2$ and standard bicarbonate

Arterial blood samples were obtained from a polyethylene catheter in the brachial artery or the radial artery. The catheter was introduced with the method described by Berneus, Carlsten, Holmgren & Seldinger (1954). During the operations a continuous check on the blood pressure was made possible by connecting up the catheter with a

end of the operation the oxygen saturation had increased to 95 %. As the spontaneous ventilatory functions of this patient might be expected to be insufficient postoperatively a tracheotomy was performed and the patient given artificial ventilation with the respirator for two days after the operation. During this period the values for $PaCO_2$ were within normal limits when the same amount of ventilation as that used during the operation was applied. Case no. 1, a patient with thoracic wall resection, was also given postoperative artificial ventilation for 4 days. This patient manifested mediastinal flutter and the function of the remaining lung was also decreased.

pH and standard bicarbonate

pH shows slightly alkalotic values in most of the patients, indicating relative hyperventilation. During the operation pH decreases, which according to the figures given in Table 3 may be interpreted as due to somewhat increasing values for $PaCO_2$ as compared with the preoperative values. The standard bicarbonate values are within normal limits preoperatively, but show a tendency to decrease during the operation, indicating an accumulation of acid metabolites. The difference between the preoperative values for standard bicarbonate and those obtained at the end of the anesthesia amounts to 2.7 ± 1.2 MEkv/l (difference between means $\pm$ standard error) and is probably significant ($P < 0.05$–0.02).

DISCUSSION

Retention of carbon dioxide due to inadequate alveolar ventilation has long been considered to be one of the greatest dangers connected with intrathoracic operations. Giertz (1916) was probably one of the very first to attempt a methodical investigation of the ventilation changes in different degrees of pneumothorax, and he was able to establish the fact that when pressure-differential respiration according to Sauerbruch was applied there was a great reduction of the respiratory minute volume. Thus after the application of pressure-differential respiration non-thoracotomized patients in the waking state experienced a strong oxygen-hunger. Giertz had no possibility of carrying out gas analyses; but it is completely clear and has, moreover, subsequently been shown by Crafoord (1938) that pressure-differential ventilation gives rise to a pronounced carbon dioxide retention leading to the death of the animal or of the patient unless better ventilation is brought about. Crafoord (1938) was able to show clearly that a marked *hyperventilation* brought about with a mechanical ventilation apparatus was not injurious for the patients, and that, on the contrary, it was a great advantage in intrathoracic operations. Respiratory acidosis connected with intrathoracic operations has since been treated by a large number of writers (Beecher & Murphy, 1950; Nealon, Haupt, Price & Gibbon, 1955; Allbritten, Haupt & Amadeo, 1954), all of whom have drawn attention to the difficulty of bringing about adequate ventilation. Nealon, Gibbon & Price (1958) studied the effect upon the ventilation exercised by the body-position in thoracotomies, and found, *inter alia*, that the posterolateral position required

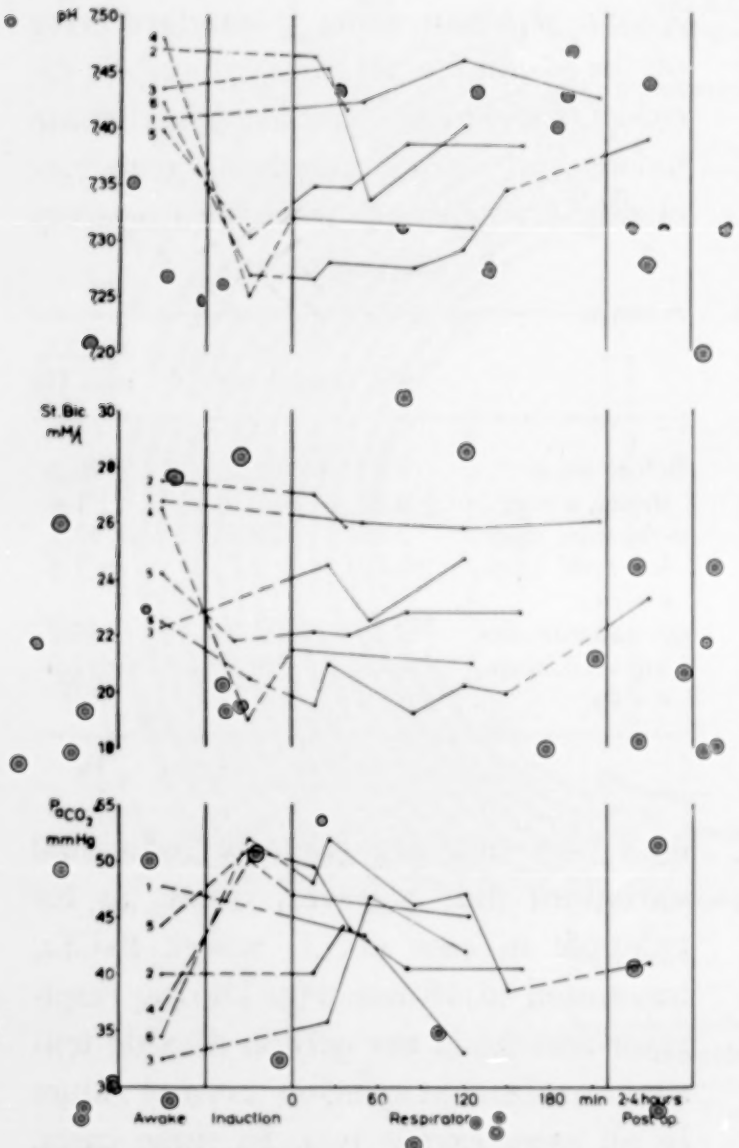


FIG. 2. pH, $PaCO_2$ and standard bicarbonate before, during and after anesthesia where mechanical ventilation with the Engström respirator has been used. The patients were operated upon for pathological processes of the lungs.

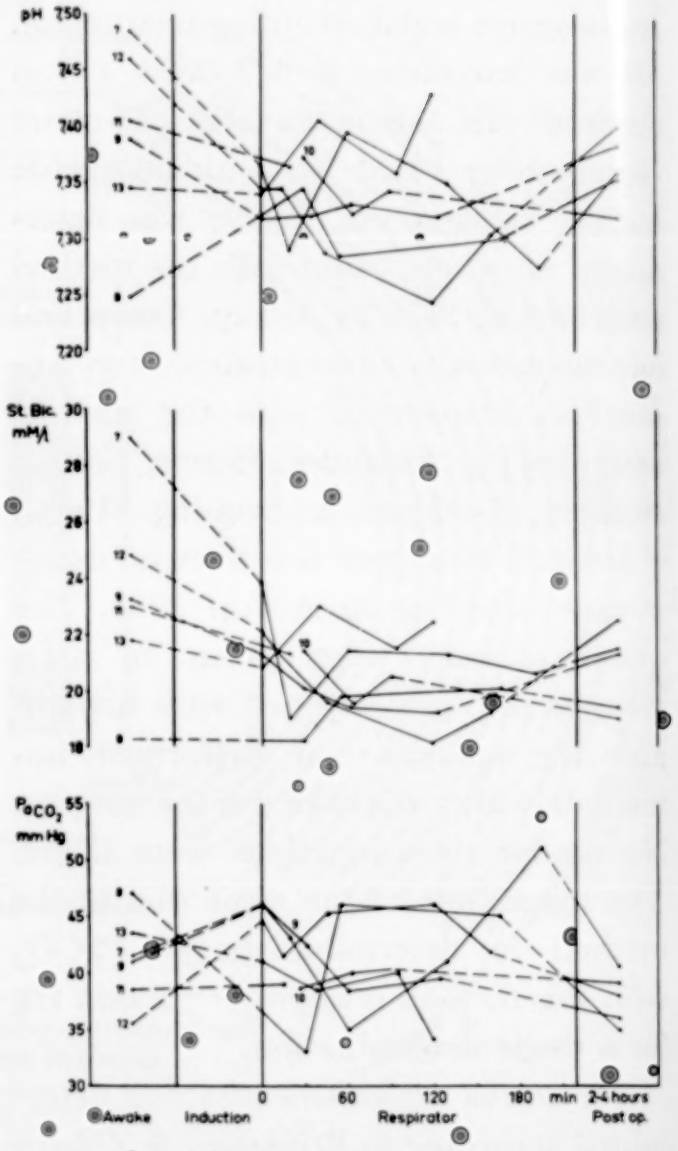


FIG. 3. pH, $PaCO_2$ and standard bicarbonate before, during and after anesthesia where mechanical ventilation with the Engström respirator has been used. The patients were operated upon for pathological changes of the heart or the great vessels. Patient No. 7 also had marked changes in pulmonary function.

saturation could not be raised to more than 88 % at any time throughout the anesthesia despite ventilation with 50% oxygen. Even the preoperative value for the oxygen saturation with air respiration was low, viz. 84 %. In the other cases one may observe a certain tendency to hyperventilation, with a lowest obtained $PaCO_2$ value of 33 mm Hg in case no. 1. This value was obtained at the end of the operation, when the pathological lung process had been removed.

In case no. 7, a patient with a constrictive pericarditis and severe right heart insufficiency, the lungs were heavy and edematous. It was difficult to obtain good oxygenation once the pneumothorax was established, and arterial oxygen saturation values of 74 % were observed. These persisted during the period of removal of the calcified pericardium; but the carbon dioxide tension was normal, thus indicating that the alveolar ventilation was sufficient. By the

compliance and resistance in the respiratory passages. The semi-open system eliminates the risks connected with carbon dioxide filter and dead space is reduced to a minimum. Another factor that may conceivably contribute to a more effective ventilation is the appearance of the pressure curve during the inhalation phase. At the end of the insufflation the pressure curve has a short plateau, i.e. the pressure remains for a short time at a constant value. During this period a levelling out of volume between badly ventilated parts of the lung and parts with good ventilation can take place (Bühlman, 1958), which is particularly valuable during thorax operations, when the inferior lung is compressed through the additional weight of the mediastinum and viscera.

SUMMARY

The relationship between the pulmonary ventilation and the carbon dioxide tension of arterial blood during thoracic anesthesia has been investigated in 13 patients. The ventilation has been administered with the Engström respirator, a volume-cycled, intermittent positive-pressure apparatus working with a semi-open system. The ventilation has been calculated from a ventilation nomogram constructed for the apparatus by Engström & Herzog.

In six patients with normal lungs on whom operations on the heart and the great vessels have been performed a slight hyperventilation has been evident. In no patient has inadequate alveolar ventilation been established. In a group of seven patients with preoperative signs of very impaired ventilatory function the ventilation administered has been adequate in six patients. One patient, however, showed a slight increase in the carbon dioxide tension up to 49 mm Hg, and the ventilation was therefore increased by 25 %, which reestablished normal carbon dioxide values.

pH and standard bicarbonate have shown changes explainable as due to slight hyperventilation and a mild accumulation of acid metabolites.

The ventilation nomogram may be safely used for the calculation of the ventilation to be applied during intrathoracic operations. In patients with pathologic processes of the lungs which it is intended to remove surgically and with very impaired ventilatory function it may be advisable to increase the total ventilation by 10 to 20 %.

The discrepancy between the amounts of ventilation applied per minute in this series and those given in the literature, which latter are about twice as large, is explained as due to the superior construction and functioning of the respirator used in our investigation.

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higher ventilation than did the antero-lateral. The interesting point in these works, however, is the order of magnitude of the ventilation actually applied to the patients. This is in general a matter of 14–17 l/min., or 10–11 l/min. per m^2 body-surface, which deviates considerably from what one finds in spontaneously breathing patients. These high ventilation figures also deviate markedly from those we have been able to observe when using the Engström respirator.

As appears from the results, the administered volumes calculated from the nomogram are in good agreement with the ventilation requirements of the patients. This is especially striking in the case of operations on heart and vessels, where the lung functions are preoperatively normal. A certain *hyperventilation* is even observable in these cases. In cases with primary lung affections the results do not show such good agreement and a greater variation is observable for the $PaCO_2$ values obtained. This must of course be seen against the background of the severe affections treated, which themselves give rise to pathological changes in the gas exchange. It may, however, be confidently stated that the Engström–Herzog nomogram is on the whole applicable in these cases, and if certain corrections with reference to the state of the lungs are made one is fully justified in using it.

To what, then, is due the discrepancy between the ventilation volumes we have been able to administer to our patients with retained or somewhat subnormal $PaCO_2$ values, and those one finds in the literature? The most important cause is probably to be sought in the great difference in the mode of administration of the ventilation. The American writers have as a rule used conventional anesthetic apparatuses with carbon dioxide-filter in a semi-closed system, where the respiratory bag is replaced with a device for mechanical compression with a construction similar to that of AGA's spiropulsator (Jefferson Ventilator). These types of apparatus are pressure-cycled and the ventilation administered will depend on the resistance in the respiratory passages and on the elastic properties of the lungs (Elam, Kerr & Janney, 1958); and it is difficult to administer a constant minute volume. The presence of a carbon dioxide filter in a semi-closed system will influence the concentration of CO_2 in the inhalation gas, so that if the filter does not function absolutely perfectly, or if the valves have any back-leakage there will be increased CO_2 concentrations, which require a higher minute ventilation. Anesthetic apparatuses of conventional type are provided with elastic rubber tubes to be connected up with the patient. These elastic rubber tubes are dilated during the insufflation phase and a considerable part of the respiratory volume administered from the respiratory bag is never made available to the patient but runs off through the exhalation valve. If the amount of gas passing through the latter is measured with a gasometer this will record bigger volumes than have reached the patient's lungs. In the Engström respirator all these undesirable factors have been eliminated. Thus the apparatus functions on the volume principle and the administered amounts are consequently independent of changes in

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From the Royal Swedish Air Force Medical Examination Center, Stockholm, Sweden

Ventilation Nomogram for Practical Use with the Engström Respirator

C.-G. Engström and P. Herzog

In case of prolonged artificial respiration with a respirator the effect of ventilation must be accurately adapted to the individual's metabolism for the adequate elimination of the carbon dioxide produced and in order to avoid the risks of both hypo- and hyperventilation.

Through analysis of the carbon dioxide tension of arterial blood and alveolar air one can, certainly, get information concerning the status of the patient's ventilation at the time when the sample is taken. Some apparatuses also permit continuous recording of the carbon dioxide; but the methods applied here are usually complicated, and are suitable only for checking, not for routine control, of the artificial respiration.

With the Engström Respirator (Fig. 1) (Engström, 1953, 1954; Cara, 1954; Björk, Engström, Friberg, Feychting & Swensson, 1956; Cara, Rudler, Angles & Fourcade, 1957; Jouasset, 1957) it is possible to administer an accurately adjustable ventilation effect which is kept constant independently of changes in the respiratory resistance. This actualizes the need to be able to calculate, simply but with sufficient accuracy, the ventilation which in the individual case is to be set on the respirator in order to obtain adequate alveolar ventilation.

Ventilation standards for use in cases of prolonged artificial respiration have previously been published by Radford (1955), who has also discussed in detail the principles for the calculation of these standards.

With the standards in question the ventilation required for the maintenance of normal Pa_{CO_2} is calculated from data concerning the patient's weight, sex, and respiration frequency. Corrections for "daily activity, fever, altitude, tracheotomy and metabolic acidosis during anaesthesia" are also given.

Together with spirometric determination of the respiratory volume the standards in question admit of a control of the adequacy of ventilation in treatment with body respirators. With systems operating with positive pressure the values calculated from these standards cannot, however, be used directly, so

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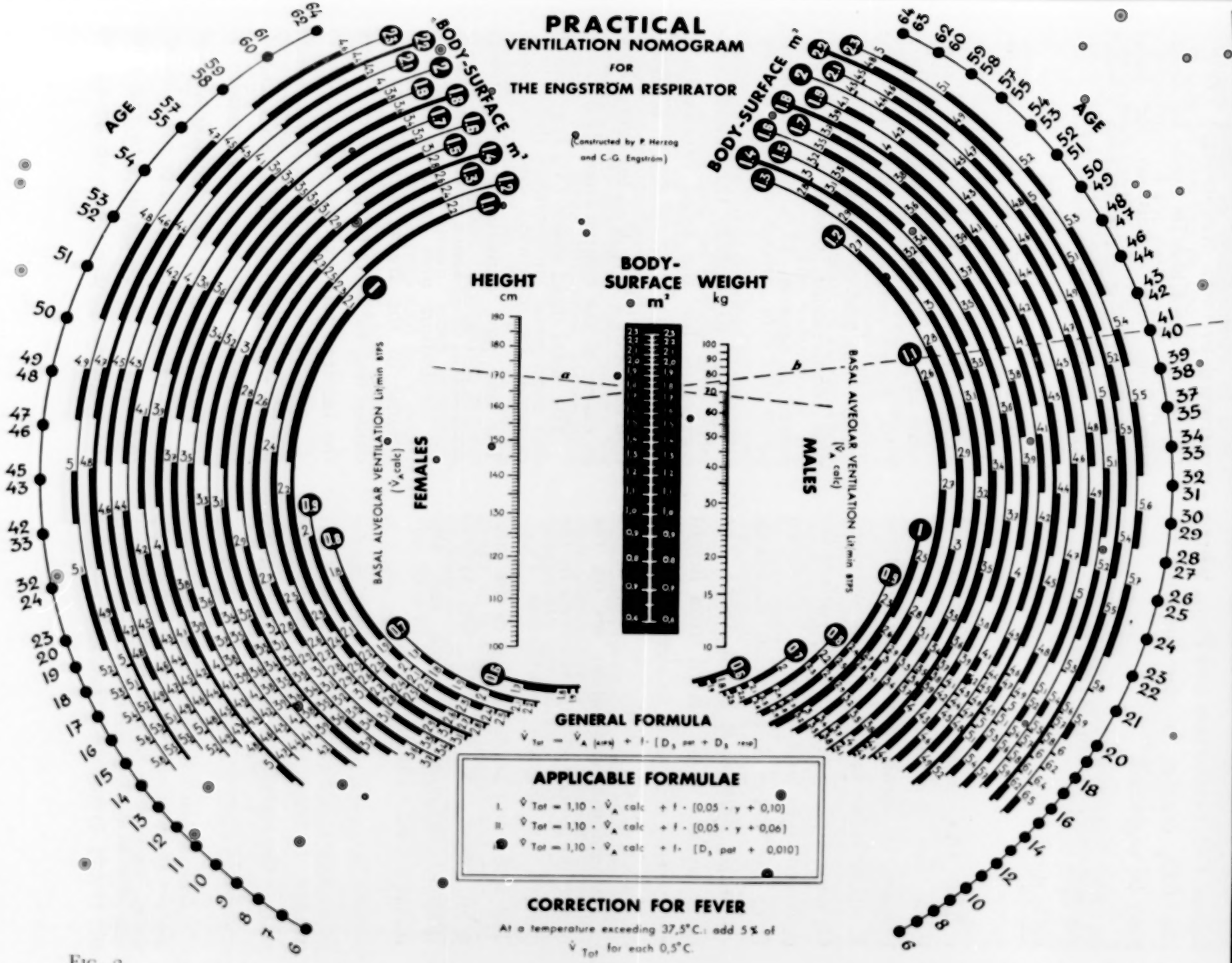
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PRACTICAL
VENTILATION NOMOGRAM
FOR
THE ENGSTRÖM RESPIRATOR

(Constructed by P. Herzog and C.-G. Engström)



GENERAL FORMULA

$$\dot{V}_{Tot} = \dot{V}_A \text{ (calc)} + f \cdot [D_s \text{ pat} + D_s \text{ resp}]$$

APPLICABLE FORMULAE

I. $\dot{V}_{Tot} = 1{,}10 \cdot \dot{V}_A \text{ calc} + f \cdot [0{,}05 \cdot y + 0{,}10]$

II. $\dot{V}_{Tot} = 1{,}10 \cdot \dot{V}_A \text{ calc} + f \cdot [0{,}05 \cdot y + 0{,}06]$

III. $\dot{V}_{Tot} = 1{,}10 \cdot \dot{V}_A \text{ calc} + f \cdot [D_s \text{ pat} + 0{,}010]$

CORRECTION FOR FEVER

At a temperature exceeding 37,5°C.: add 5 % of $\dot{V}_{Tot}$ for each 0,5°C.

FIG. 2.

EXPLANATION

$\dot{V}_{Tot}$ = the total ventilation litre per minute to be adjusted on the respirator. Calculated on a calm patient without fever.

$\dot{V}_A$calc = the alveolar ventilation calculated by means of the nomogram litre/min. (B T P S).

f = respiration frequency per minute (adjusted on the respirator).

y = body-surface in m².

$D_s$pat = the dead space of the patient after tracheotomy, in liters, $D_s$pat = 0,05 · y (with the body-surface as a parameter).

1,10 · $\dot{V}_A$calc = includes the correction of $\dot{V}_A$calc to 24°C., and a correction for the divergents from the standard metabolic conditions.

$D_s$resp = the "functional" dead space of the respirator in liters when using different apparatus tubes:

I [0,10], II [0,06], III [0,010], respectively.

APPLICATION

1) calculate y from height and weight (example line a)
2) calculate $\dot{V}_A$calc from y, age and sex (example line b)
3) place the values of $\dot{V}_A$calc and y in the formulae I, II or III, where I is to be used for standard apparatus tubes (large-size), II for micro-tubes and III when the micro-tubes are connected by-passing the humidifier directly to the valve-box.

EXAMPLE

Male patient: height 170 cm. weigth 68 kg. will give a body-surface of 1,8 m². At the age of 40 years, $\dot{V}_A$ calc is found to be 4,2 l/min.

To get $\dot{V}_{Tot}$ proceed as follows: The body-surface (y) was found to be 1,8 m².
Assuming the frequency (f) to have been set at 20 cycles per minute and that standard apparatus tubes are used (formula I), then $\dot{V}_{Tot}$ in liters per minute will be:
1,10 · 4,2 + 20 · [0,05 · 1,8 + 0,10]
= 8.420 lit/min.

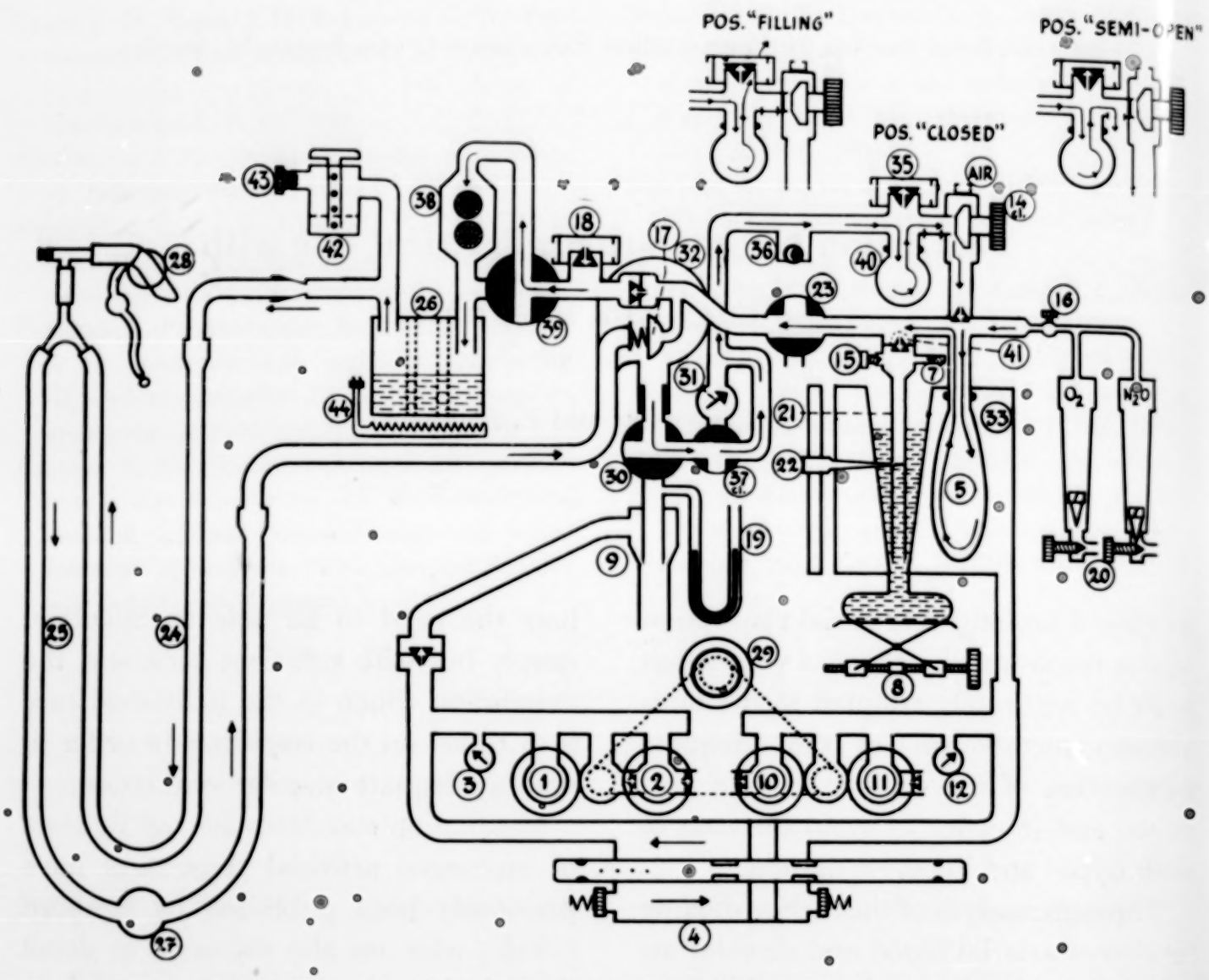


FIG. 1. Diagram of the Engström Narcosis Respirator, model 200. The diagram shows the principles of the Engström Respirator with setting of the valves for closed system. The two inset detail sketches show the two other valve positions "semi-open" and "filling". These are operated by the lever on the rim of the dosage valve.

corrections must also be made for the dead space of the apparatus and for volume lost in consequence of compression of the gas in the system, whose compressible volume must thus be known.

The practical ventilation nomogram for the Engström Respirator presented here contains correction factors for the apparatus under different conditions and has different bases for the calculation of dead space, but is in other respects calculated in a way similar to that for Radford's ventilation standards.

PRINCIPLES FOR THE CONSTRUCTION OF THE NOMOGRAM

The nomogram (Fig. 2), which is designed for the maintenance of normal $Pa_{CO_2} = 40$ mm Hg, is derived from the standard metabolism for individuals of both sexes from the ages of 6 to 64 years and the variations in the height and weight occurring in practice. It consists of two parts, a general part for calculation of the alveolar ventilation requirement in liters per minute BTPS under basic conditions, here called $\dot{V}_A$ calc, and

correlation to the body surface (y) if the calculation is carried out according to the following simple formula:

$$D_s pat \text{ (in liters)} = 0.05 \cdot y.$$

The second part of $V_D Tot$ consists of volume losses in consequence of compression of the gas in the positive pressure system of the respirator and in the connecting tubes. This "functional dead space" of the respirator, which in the nomogram is referred to as $D_s resp$, varies with the total compressible volume of the system and with the pressure, just below "peak pressure", where the expiration valve opens. This "peak pressure" has in practice been found in different patients to remain fairly constant about a mean value of 20 cm H_2O. From the compressible volume of the system, which is known, and this mean "peak pressure" it is possible to calculate $D_s resp$ according to Boyle's law. After the addition of 20 ml for loss of volume in the water manometer and mean "peak pressure" = 20 cm H_2O, the values for $D_s resp$ for three different alternative tubes with connections have been calculated in liters as I = 0.10, II = 0.06, III = 0.010. In case of possible greater deviations in the mean "peak pressure" these values for $D_s resp$ can be directly corrected on the basis of the observed "peak pressure".

On these bases for calculation one may derive the following general formula:

$$\dot{V}_{Tot} = \dot{V}_{AR} + f \cdot [D_s pat + D_s resp]$$

from which formulas for practical application of the nomogram are derived.

$$\text{I. } \dot{V}_{Tot} = 1.10 \cdot \dot{V}_A calc + f \cdot [0.05 \cdot y + 0.10]$$

$$\text{II. } \dot{V}_{Tot} = 1.10 \cdot \dot{V}_A calc + f \cdot [0.05 \cdot y + 0.06]$$

$$\text{III. } \dot{V}_{Tot} = 1.10 \cdot \dot{V}_A calc + f \cdot [D_s pat + 0.010]$$

DISCUSSION

In cases requiring prolonged artificial respiration the CO_2 production does not undergo great or rapid changes, and the ventilation requirement thus remains fairly constant. The possibility of administering a stable ventilation calculated according to the actual requirement is therefore of the greatest practical importance. In the construction of a ventilation nomogram for clinical use it is necessary to meet both the demand for reliability of the calculated values and practical demands for ease of comprehension. For the nomogram to be suitable for practical use, the calculations must be based upon easily available data concerning the patient and must not necessitate complicated calculating operations. In the construction of the nomogram it is therefore necessary to make certain simplifying approximations, and the reliability of the nomogram will in a high degree depend on the way in which these are made. The nomogram has been in clinical use since February 1957, and frequent control analyses of arterial carbon dioxide tension from many patients receiving artificial respiration both postoperatively as well as during anaesthesia have shown that they have been given an adequate alveolar ventilation (Friberg & Widman,

a special part with "applicable formulas" containing correction factors for obtaining the corresponding total ventilation values, $\dot{V}_{Tot}$, in liters per minute to be set on the respirator.

The calculation of $\dot{V}_A$ calc is based on the relation between the alveolar ventilation, CO_2 production and Pa_{CO_2}, where the CO_2 content in the inspired air may be neglected:

$$\dot{V}_A \text{ calc (ml per min. BTPS)} = \frac{CO_2 \text{ prod. (ml per min. STPD)} \times 863}{Pa_{CO_2}}$$

The CO_2 production is calculated from the standard consumption of oxygen, a mean respiratory quotient R = 0.82 being presumed. The standard O_2 consumption per m^2 body surface for different ages and sexes is calculated from the Mayo Foundation standards (Boothby, Berkson & Dunn, 1936). The body surface is calculated from height and weight according to the nomogram of DuBois (1915, 1916).

The minute ventilation set on the respirator is only in part received by the patient as alveolar ventilation ($\dot{V}_A$). The rest is lost as ventilation of the total dead space (V_D Tot) of the system (patient + apparatus), which can also be expressed with the formula:

$$\dot{V}_{Tot} = \dot{V}_{AR} + f \cdot (V_D \text{ Tot}),$$

where f = respiration frequency, and $\dot{V}_{AR}$ = the alveolar ventilation to be given by the respirator.[1]

[1] The difference in volume depending on difference in water vapor saturation between the preset gas entering the respiration bag and this gas after humidification being administered to the patient is small and is therefore neglected.

If adequate alveolar ventilation is to be administered, $\dot{V}_{AR}$ must coincide with the alveolar ventilation requirement, i.e. produce Pa_{CO_2} = 40 mm Hg. In calculating $\dot{V}_{AR}$, which constitutes gas of ambient temperature and pressure, from the value for $\dot{V}_A$ calc, the gas must be corrected to room temperature (24°C). Correction must also be made for deviation from the conditions for basal metabolism. For patients with normal body temperature (temp. < 37.5°C) one reckons with a standard addition of approx. 15 % to the alveolar ventilation. Together, these corrections give for the calculation of $\dot{V}_{AR}$ from $\dot{V}_A$ calc a common approximative correction factor = 1.10. Fever entails an increase of the metabolism and of the alveolar ventilation requirement, which may be estimated as approx. 13 % of every degree C.

In order to simplify the calculations, correction for the total ventilation is made, and this corresponds to an addition of about 5 % to $\dot{V}_{Tot}$ for every 0.5°C in excess of the temperature 37.5°C.

The total dead space (V_D Tot) can in principle be separated into two parts. The one part consists of the patient's anatomical dead space after tracheotomy or intubation and includes also the volume in the tracheal tube and the connecting tubes up to the Y-tube, where the inspired and expired gas divides to go different ways. This volume, which in the nomogram is designated D_s pat, varies chiefly with factors pertaining to the patient. It must be calculable without complicated measurements or calculating operations. According to our own investigations there seems to be a good

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Bronchial Involvement in Intrathoracic Sarcoidosis

C.-A. ADAMSON and E. CARLENS

Until recently, bronchial involvement has been considered a rare phenomenon in pulmonary sarcoidosis. Benedict & Castleman (1941) and Olsen (1946) each described a case with bronchoscopically observed changes, in which biopsy showed sarcoidosis. It has also been stressed as remarkable that obstruction of the trachea or bronchi is practically never seen in cases with extensive pulmonary lesions, or with large hilar lymphomas. Thus, Hodgson & Woolner (1954) wrote: "Bronchoscopy is of little value in the diagnosis of pulmonary sarcoidosis, except in eliminating other conditions from consideration." Löfgren & Lundbäck (1952), on the other hand, stated: "Bronchoscopy has proved a further aid in improving the diagnostic procedure of sarcoidosis, 5 cases out of 23 subjected to examination with this method yielding positive biopsies of bronchial mucosa or pulmonary parenchyma." In 15 of these cases, only portions of the bronchial wall were removed, whereas in 8 cases a small specimen was taken from the pulmonary parenchyma as well. Histopathologic changes typical of sarcoidosis were present in one of the former specimens and in four of the latter. This is interesting, since no data were given regarding the eventual presence of macroscopic bronchial changes, and the cases formed part of a large series of bilateral hilar lymphoma without stated pulmonary lesions.

Similar observations were made by Scadding (1956) and Citron & Scadding (1957). The latter authors found marked changes, verified by bronchography, in 3 cases. Kalbian (1957) found microscopic sarcoidosis changes in the bronchial mucosa in 6 of 11 cases examined. Kahn & Siltzbach (1958) observed red, swollen mucosa in the orifice of the middle lobe bronchus at bronchoscopy in one case. Microscopic sections showed that the submucosa was infiltrated with typical sarcoidosis lesions, which remained unaltered during more than 5 years' observation. The bronchogram disclosed bronchiectasis peripheral to these changes. These authors had an additional case with macroscopic sarcoidosis lesions of the bronchi, and 5 cases with sarcoid follicles in the submucosa of major bronchi, although the gross appearance was not remarkable. They concluded that involvement of major bronchi in sarcoidosis is more common than supposed. The authors also described sarcoid granulomas in small bronchi from lung

1937; Norlander, Pitzele, Edling, Norberg, Crafoord & Senning, 1958; Beckman, Norlander & Widman, this volume, p. 27).

SUMMARY

A ventilation nomogram constructed for practical clinical use in cases of prolonged artificial respiration with the Engström Respirator is presented. The nomogram affords the possibility of calculating the minute ventilation to be set on the respirator in order to obtain adequate alveolar ventilation in the treatment of patients aged from 6 to 64 years. The principles for the construction of the nomogram are discussed.

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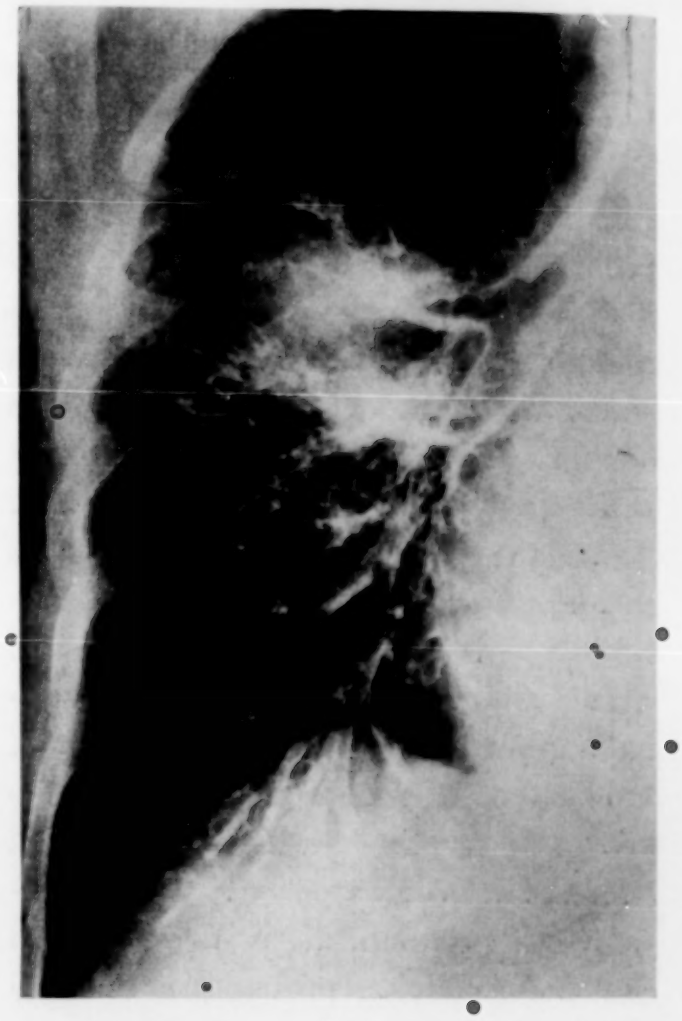
At bronchoscopy, funnel-shaped stricture of the right main bronchus was visible below the origin of the upper lobe bronchus; only an opening about the width of a lead pencil remained. The gross appearance of the mucosa at this site was completely normal, but a biopsy specimen showed histopathologic signs of sarcoidosis. Prescalene node biopsy confirmed the diagnosis. Among the findings at functional investigation were MBC 55 l/min. Bronchospirometry showed poor function of the right lung. Vital capacity: left 84.5 %, right 15.5 %. O_2 uptake: left 93.4 %, right 6 %.

In view of the recurrent infections and unilateral localization, right-sided pneumonectomy was performed on March 26, 1958. Histologic examination of material removed at operation showed sarcoidosis, with focal and miliary lesions of the lungs and bronchi. The bronchi were stenosed to a varying degree.

Case 2.—A 48-year-old farm worker, previously healthy. Mass chest radiography in September 1958 showed an infiltration in the right lung. Tuberculin positive. He was admitted to a sanatorium. Since some bronchostenosis was observed, the patient was sent to the Medical Thoracic Clinic with the tentative diagnosis of a malignant tumour of the right lung.

Roentgenologic examination (Dec. 3, 1958): diffuse, partly confluent parenchymal infiltrations in large parts of the upper lobe of the right lung. Bronchoscopy: slight, diffuse reddening of the mucosa of the right main bronchus. No visible tumour. Otherwise, nothing pathologic. Microscopic examination of a biopsy specimen from the orifice of the upper lobe bronchus gave no definite information, but the presence of a bronchial adenoma of carcinoid type was presumed. A biopsy specimen taken at renewed bronchoscopy from apparently completely normal mucosa in the upper lobe bronchus showed histopathologic signs of sarcoidosis. Prescalene node biopsy verified the diagnosis.

Bronchographic examination of the right lung (Fig. 2) showed somewhat funnel-shaped, irregular stenosis of the upper lobe bronchus, about 1 cm from its division into segmental bronchi. In addition, the anterior segmental bronchus was obliterated. The bronchographic features were regarded to be indicative of constriction by a tumour. Despite certain indications of sarcoidosis with bronchial stricture, it was considered that the presence of a tumour could not be ruled out with certainty. The patient was therefore transferred to the Surgical Thoracic Clinic, where excision of the upper lobe of the right lung was performed on Dec. 30, 1958. Histologic examination of material removed at operation verified the diagnosis of bronchopulmonary sarcoidosis.



Case 2.—Bronchography right lung. The bronchus of upper lobe constricted to funnel shape and the anterior segment bronchus entirely occluded.

Postoperative bronchography of the left lung showed a number of variations in size of the bronchial lumen of the type observed in sarcoidosis. The patient was discharged free from symptoms on Jan. 31, 1959.

DISCUSSION

Bronchoscopy is, in fact, usually indicated in the presence of uncertain pul-

biopsy in two cases. Autopsies are rare in the acute stage of this disease, but—judging by the old fibrotic cases—the pathologic findings in the lung seem to be localized chiefly to the interstitial, perivascular and peribronchial tissues.

In recent years, we have generally performed both bronchographic and bronchoscopic examination in the investigation of cases of pulmonary disease. Like several other authors, we have then observed variations in the lumen of the bronchi in many cases of sarcoidosis without fibrotic changes, for the first time in 1955. At bronchoscopy, it has sometimes been possible to observe these changes, whereas in certain cases only mucosal reactions were seen, and in others the appearance was entirely normal. Histologic examination of biopsy specimens taken at bronchoscopy has not infrequently verified the diagnosis of sarcoidosis. A remarkable fact is that this applied even in some cases in which no gross changes could be observed.

In the two cases described in the following, the investigation led to intrathoracic operation.



Case 1.—Bronchography right lung. Circular constriction of the main bronchus. Bronchus of the intermediate lobe obliterated. Lumen variations of other bronchi above all in the inferior lobe.

CASE REPORTS

Case 1.—A 50-year-old woman, earlier mainly healthy. Mantoux test negative (1 mg). In the spring of 1957, she had a dry cough and marked dyspnoea, and in June periods of fever which, after roentgenologic examination, were interpreted as right-sided bronchopneumonia. She subsequently had three similar febrile episodes, and increasing dypsnoea. In December 1957, bronchostenosis with atelectasis appeared in the right middle lobe, and bronchiectatic changes in the lower lobe.

On examination at the Medical Thoracic Clinic in January 1958, the patient's general condition was good, but she had marked dyspnoea in the recumbent position and on exertion. Roentgenologic examination showed hilar enlargement on the right side, as well as stenosis of the right main bronchus below the origin of the upper lobe bronchus. The middle lobe was atelectatic. These findings were confirmed by bronchography (Fig. 1); circular constriction of the right main bronchus was present about 1½ cm below the origin of the upper lobe bronchus. The middle lobe bronchus was obliterated. The lower lobe bronchi exhibited changes in the form of great variations in size of the lumen, with both stenosis and areas of dilatation. Variations in size of the lumen were also observed in the upper lobe bronchus.

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Investigation on the Bacterial Flora in the Bronchi in Cases of Pulmonary Tuberculosis

S. Bergqvist and F. Hagerman

In connection with an investigation on the occurrence of tubercle bacilli in resected lung tissue, non-specific bacteria were practically never found, despite the fact that the samples had not been acid-treated before the inoculation on the Dubos and Löwenstein substrate. The reason for this may have been due to the circumstance that before the operation the patients had been treated with streptomycin or to the unsuitability of the substrate in question for the demonstration of other bacteria than tubercle bacilli. On the other hand, there was, of course, the possibility that in these patients with pulmonary tuberculosis the bronchial mucous membrane was as a rule sterile. To investigate this problem bacteriological studies were carried out on bronchial secretion from patients in connection with bronchoscopy and from lung resection specimens.

TECHNIQUE AND MATERIAL

When the bronchoscope is pushed down, there is formed at its aperture a bed of mucus which contains bacteria of the mouth cavity and the throat. If bronchial swabs are taken with the help of an ordinary probe, the end wrapped with cotton-wool will practically always be contaminated with this mucus. For this reason a swab-carrier was constructed. This was guided in the centre of the bronchoscope with the aid of thin steel springs which were soldered on. (Fig. 1.) In this way it was possible to avoid a contamination by bacteria of the mouth cavity and throat. The springs did not obstruct the view, and it was thus possible under direct control of the eye to take samples of bronchial secretion from suitable bronchial sections. Samples were taken from 45 cases with active pulmonary tuberculosis, to 12 of whom antibiotics had been administered before the bronchoscopy.

As soon as the lung specimen had been resected during the operation, at least two swabs were taken from the bronchi. Thirty-nine specimens were examined from the same number of patients with current pulmonary tuberculosis, all of whom had received streptomycin before the operation.

All specimens were plated on the following media: two blood agar plates for aerobic and anaerobic incubation, one blood agar plate with a streak of *Staphylococcus pyogenes* to show the

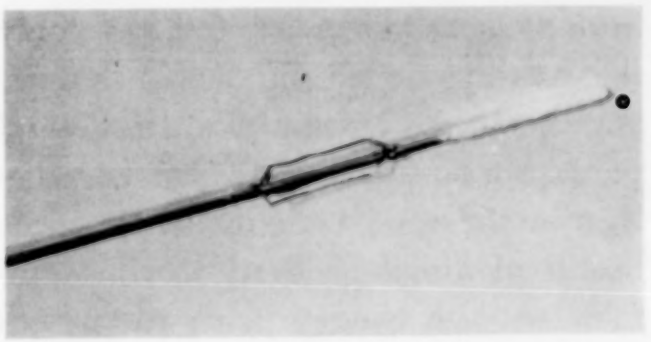


Fig. 1. Apparatus for bronchial swabs.

monary disease. It is therefore of some value when sarcoidosis is suspected to be acquainted with the microscopic changes in the bronchi even with a normal gross appearance. The chances of a positive diagnosis are probably increased if a biopsy specimen is taken from several sites in the bronchial tree. Kalbian has stated that it is reasonable to take the specimen from the bronchus draining the area which, on the roentgenogram, shows the maximum disease. By this means, prescalene node biopsy or mediastinoscopy may be rendered superfluous.

It is difficult to determine the functional implications of the bronchial changes. It is true that emphysema occurs, but—according to Marshall *et al.* (1958)—the decrease in ventilatory capacity is seldom as pronounced as the defect in diffusion capacity, probably caused by obliteration of the fine vessels. Moreover, bronchial stricture usually leads to bronchiectasis, which is considered to be rare in sarcoidosis. Consequently, it seems likely that the bronchial lesions—like sarcoidosis lesions at other sites in the body—heal relatively without traces in many cases. That they may, however, persist can be inferred from the cases reported here. It is also highly probable that they are actually primary bronchial changes and not, as has been believed earlier, secondary lesions on the basis of fibrosis and shrinking of surrounding tissues.

SUMMARY

An account is given of two cases of bronchopulmonary sarcoidosis. In one case, in which the changes included circular stenosis of the main bronchus and obliteration of the middle lobe bronchus, right-sided pneumonectomy was performed. In the other case, in which one of the features was funnel-shaped stenosis of the upper lobe bronchus on the right side, operation consisted of excision of the right upper lobe.

In both cases, examination of a biopsy specimen from apparently completely normal mucosa disclosed pathohistologic lesions indicative of sarcoidosis.

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was introduced through the pharyngeal tube in anesthetized patients. In this connection he found that patients with healthy respiratory passages had a sterile bronchial secretion. It was, moreover, possible to show that asthma patients not infrequently lacked bacteria in the bronchi. Later, in connection with bronchoscopy, Brumfitt and co-workers introduced a specially constructed carrier into the bronchi and took samples of secretion without contamination with bacteria from the mouth cavity and throat. They examined 42 persons with healthy lungs, all of whom had sterile bronchial secretion, in spite of the majority of them harboring one or several of the commonest kinds of pathogenic bacteria in the mouth cavity or throat. On the other hand, of 27 patients with chronic bronchitis (with or without bronchiectasis), every one had pathogenic bacteria in the bronchial secretion. The commonest infectious agents were *Hemophilus influenzae*, in 18 cases, pneumococci, 4 cases, coliforms, 4 cases and, finally, β-streptococci in one case. The same writers also showed that with simultaneous examination of sputum and pharyngeal samples it was possible to get some idea of the bronchial infection. In those cases in which pathogenic bacteria were shown to be present in sputum but not in the pharyngeal sample, it was probable that these bacteria derived from a bronchial infection. Tunevall and Wasserman, on the other hand, found in certain cases pathogenic bacteria in bronchial secretion collected in the ordinary way, but not in sputum from the same patient. According to May, this may be explained by the fact that different portions of sputum may contain different bacteria. This writer therefore draws attention to the importance of making simultaneous cultures from several samples of sputum.

Investigations on the bacterial flora of the bronchi in cases of pulmonary tuberculosis with the help of an improved technique of sample-taking in connection with bronchoscopy have not, as far as we are aware, been previously published. Palva and co-workers, however, brought up bronchial secretion with suction and in 131 examinations of cases of pulmonary tuberculosis they found bacteria 128 times, though in general only apathogenic bacteria. However, in seven cases *Staphylococcus pyogenes* was shown, in three pneumococci, in six *Haemophilus influenzae* and in seven cases *Proteus*, though not in pure culture. This was of course underlined as a noteworthy fact, in consideration of the general abundant occurrence of bacteria. The conclusion arrived at, however, was that tuberculous disease of the lung probably damages the bronchial mucous membrane, so that commensal bacterial flora in the mouth cavity and throat could wander down and infect the bronchial tree. What appears to us most probable, however, is that these bacteria had been carried down in the bronchial tree in connection with bronchoscopy, and thus constituted a contamination. The correctness of the results found by us is also favoured by the circumstance that it is only rarely that one sees any effect of non-specific antibiotic therapy in cases of pulmonary tuberculosis even where there are caverns, fever and copious sputa.

TABLE 1. Findings of non-specific bacteria in the bronchi of 45 patients with pulmonary tuberculosis.

	No. of cases	Sputum volume per day, ml				Culture	
		0	1–5	6–25	>25	Pos.	Neg.
Treated with streptomycin	12	6	—	2	4	1	11
Not treated	33	16	9	5	3	4	29

satellite growth of *Haemophilus influenzae* and a broth tube with thioglycollate; finally, a broth type containing sodium azide for concentration.

RESULTS

In bronchial secretion taken in connection with bronchoscopy (Table 1) the result of cultivation was negative in 11 of the 12 cases that had for longer or shorter periods been treated with streptomycin before the examination. In one case a pure culture of *Staphylococcus pyogenes* (the strain was streptomycin-resistant) was found. Ten days earlier this patient had undergone resection operation combined with bronchoplasty. Among the remaining 33 cases that had not been treated with antibiotics before the bronchoscopy, β-streptococci were found in one case, mixed flora consisting of only apathogenic bacteria in two cases and, finally, mixed flora consisting of pneumococci and apathogenic bacteria in one case. Among these four cases only the last-mentioned produced sputum, and this in the amount of about 200 ml per 24 hours. It is open to question whether in the cases with mixed flora the bronchial sample had not been contaminated with bacteria from the mouth cavity and throat.

In the bronchial swabs from the 39 resection specimens no growth was obtained in 33 cases. In the remaining six there were pneumococci in two cases, *Staphylococcus pyogenes* in two (the one strain streptomycin-resistant), *Alcaligenes* sp. (streptomycin-resistant) in one and, finally, diphtheroid rods in one case. In three of these patients bronchiectasis had been diagnosed before the operation. In one of the other three there was a pronounced fibrotic tuberculosis in which bronchiectasis was probably present but in which bronchography had not been carried out. All the cases were free of sputum before the operation.

DISCUSSION

On account of the difficulties in taking samples it has not previously been possible to get a reliable notion of the bacterial flora of the bronchi. Through the so-called washing of sputum Mulder was able to show as a probability that the commonest agents of infection in cases of chronic bronchitis and bronchiectasis were *Haemophilus influenzae*, pneumococci and coliforms. Only in isolated cases did β-streptococci and pyogenic staphylococci occur. Colldahl and coworkers constructed a catheter which

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The Airway Dead Space in Tracheotomized Patients[1]

G. Birath, R. Malmberg, M. Beck and N. P. Bergh

Tracheotomy has proved to be of great value during the postoperative period following major surgical thoracic operations. By tracheotomy the patients' air passages can be kept clear much more effectively than by coughing alone. This is of special importance if the respiratory reserves are small, since impaired ventilation, due to the accumulation of secretions, may prove deleterious. In this case, tracheotomy serves also another purpose, viz. to provide an improved alveolar ventilation through a reduced airway dead space.

The aim of the present investigation is to ascertain the degree in which reduction of the dead space may take place.

METHODS

The respiratory dead space, which has been determined by this method, refers to the air passages, and is called the airway dead space, the anatomical dead space or series dead space, in order to differentiate it from physiological dead space, which includes both the airway dead space and the alveolar volume, where either no gas exchange, or only incomplete exchange, takes place as a result of reduced circulation in relation to ventilation (viz. the dead space effect).

The determination of the airway dead space was made according to the principle devised by Fowler (1948), with the continuous analysis of the N_2 content of the expiratory air after the inhalation of pure O_2. At the beginning of expiration, pure O_2 issues from the dead space; this is followed, first, by a mixture of O_2 and N_2 containing some alveolar air, and finally, by pure alveolar air.

Either a geometrical construction (Fowler, 1948) or a model experiment (Birath) may be used to subsequently determine a point on the N_2 curve, which corresponds to the dead space of the air passages, and divides the S-shaped curve between pure O_2 and pure alveolar air in a certain proportion.

The principle is illustrated by the diagram (Fig. 1) and by calculating the value of the dead space from a given curve (Fig. 2). For a more detailed description reference is made to a forthcoming publication (Birath).

When using this method, the standard error for each determination is ca. ± 10 %.

The determination was carried out as follows. A special mouthpiece, with a

[1] Supported by a grant from Statens Medicinska Forskningsråd.

SUMMARY

Through a special method it is possible to make bronchial swabs in connection with bronchoscopy without contamination with oral and pharyngeal organisms. With this method it has been shown that in cases of pulmonary tuberculosis the bronchi are as a rule sterile.

Where non-specific bacterial infections are found there is probably the complication of pronounced bronchiectasis and stenosis. This was shown by the examination of resected lung specimens.

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pulmonary-function tests showed restrictive ventilatory insufficiency. Immediate tracheotomy was performed after the long operation, because of respiratory difficulties.

B. F. Progressive symptoms of myasthenia gravis for one and a half years. Normal chest radiograms. Preoperative pulmonary-function tests revealed ventilatory insufficiency, probably due to muscular weakness, which also increased the residual volume. Thymectomy was performed on 24 February 1958. Postoperative ventilatory insufficiency was so manifest that tracheotomy was immediately performed.

Si. J. A rotundiform bronchial carcinoma, the size of an orange, in the right upper lobe; with symptoms indicating one month's duration, and a little pleural exudate. Function tests were within normal limits. Upper lobe resection on 15 December 1958. Recurrent laryngeal paralysis hindered expectoration; and therefore a tracheotomy was performed on 18 December 1958.

B. W. Right-sided, chronic apical tuberculosis with bronchiectasis and small changes in the left apex. Preoperative function tests for both lungs were within normal limits; but bronchospirometry revealed reduced vital capacity, and diminished O_2 uptake on the right side, which was only 45 % as compared with the normal 55 %. Bilobectomy (upper and middle lobe), with thoracoplasty, was performed by Björk's method on 26 January 1958. Postoperative, temporary diaphragmatic paralysis on the right side, with paradoxical breathing and expectoration difficulties; consequently, tracheotomy was performed on 28 January 1959.

H. M. Carcinoma of the thyroid gland, infiltrating the trachea; symptoms indicated 7 months duration prior to operation. Preoperative radiogram of the lungs was normal, and the function tests were within normal limits, with the exception of a diminished maximal voluntary ventilation; probably owing to tracheal obstruction. The tumour was extirpated on 4 December 1957, and tracheotomy was performed on 29 January 1958, because of tracheal stenosis that followed resection of the tumour. The patient died subsequently.

Values of the dead spaces obtained without tracheotomy are, on the whole, in good agreement with what may be expected, with regard to body weight and sex. Thus the males had the highest values. For Sv. J. and Si. J. these values are within normal limits, whereas B. F. has a surprisingly high value (247 ml BTPS). Though there is no reason to suppose that any error was made in this determination, nevertheless, no conclusions should be drawn from this exceptionally high value. The dead space was determined, without tracheotomy, for only one of the two female patients (B. W.), and was found to be within the expected range.

The values of the dead space, following tracheotomy, are all under 100 ml. Reduction in individual cases was 111, 190, 107 and 77 ml or 62, 77, 54 and 63 % respectively. Thus, as a result of tracheotomy, the dead space was reduced by about a $\frac{1}{2}$ or $\frac{2}{3}$ (possibly even more).

DISCUSSION

It is clear that the respiratory economy can profit greatly by tracheotomy. The reduction of the dead space is of particular importance under conditions where breathing volume is impaired. After major thoracic operations, by this means, a high total ventilation is often maintained, with a small breathing volume at a high frequency. With a breathing volume of 0.3 liters, for example, and a respiratory dead space of 0.150, the alveolar ventilation is only 50 % of the total. But if the dead space is reduced to 0.050, not less than 0.250 liters of the total ventilation reach the alveoli and are utilized, i.e. 83 % of the total ventilation. Consequently, tracheotomy raises the alveolar ventilation by ca. 60–70 %.

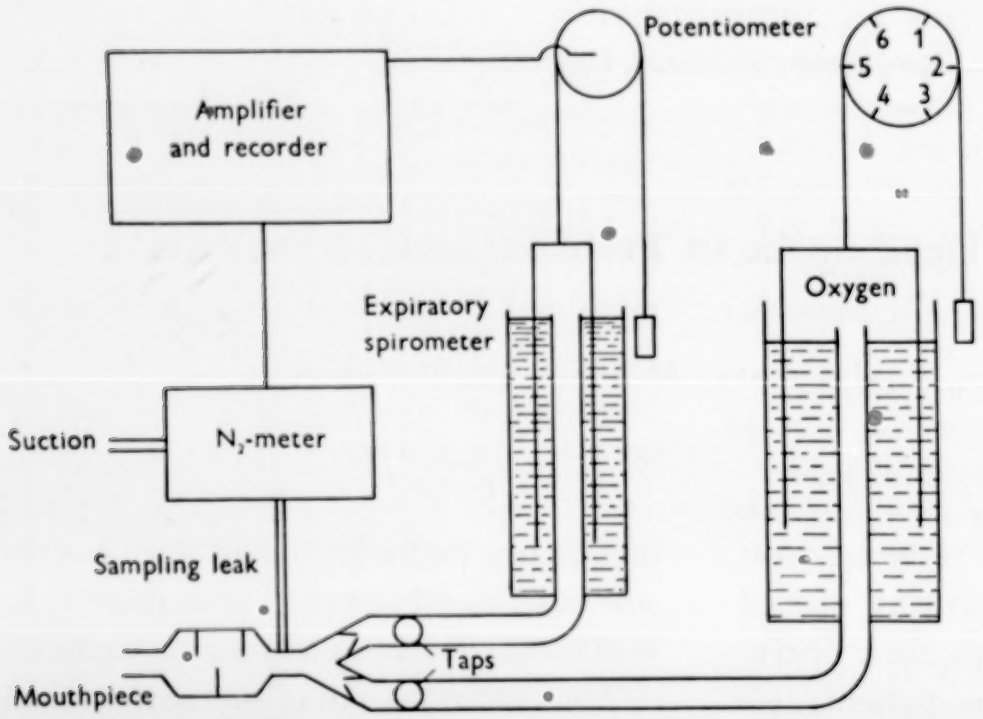


FIG. 1. Arrangement of apparatus for measurement of respiratory dead space (Fowler method).

given volume, was fixed to the tracheal cannula. The patient then inhaled about 0.5–0.7 liters of O_2 and immediately exhaled. The registrations were made while this was taking place. Any secretion found in the patient's air passages was sucked out before each determination was made. Owing to the poor general condition of the tracheotomized patients, the determinations had to be carried out while the patients were in a supine position. Any new investigations, after the tracheotomy was closed, were conducted while the patients were in a sitting posture; but in all other respects the technique was that described for patients in a supine position.

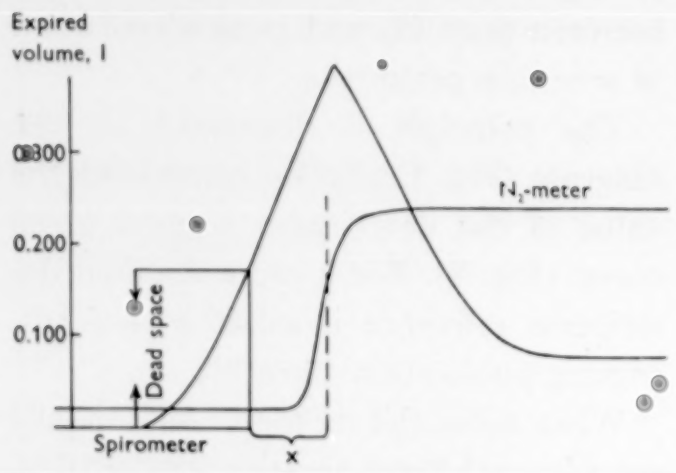


FIG. 2. Record of volume and N_2 concentration of expired gas after O_2 inhalation. ×, lag of N_2-meter; dashed line, theoretical gas front.

RESULTS

Consistent results were obtained in those cases where cooperation with the patients proved possible, and where the composition of their alveolar air was fairly uniform. In emphysematous cases, which represent a large part of the tracheotomies, the method yielded uncertain results, because of the irregular distribution of the expired air. Consequently, such cases were not investigated in this way.

Sv. J. In 1954–1955 lung changes of a sarcoid type, which were treated with X-ray on the hilar lymph nodes, and later with cortisone. In 1955 pneumonia and pleurisy on the right side. In November 1956, a large shadow of a tumour was discovered in the anterior mediastinum. This was removed surgically on 13 February 1957, and proved to be a malignant thymus. The lung radiogram was otherwise normal. Preoperative

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Surgery at the Left Bronchotracheal Junction with the Aid of Green's Tube

V. O. Björk and M. H:son Holmdahl

Resection or anastomosis at the left bronchotracheal junction may be a very trying and difficult surgical procedure. We consider these operations best performed in the face-down position and sometimes after mobilization of the aortic arch with division of the first 4 to 5 pairs of intercostal arteries. The use of a Green's tube for right-sided endobronchial anesthesia (Green and Gordon, 1957) is of great help in these difficult cases. Earlier we (Björk, 1955) used either lateral occlusion of the trachea by a Pott's or Super Satinsky clamp or intermittent occlusion of the opening into the trachea with the finger in between the placing of the sutures for the anastomosis. Now we always use the Green's tube for these cases and consider it a great improvement, with perfect anesthetic control and an unhurried surgical procedure.

TECHNIQUE

Green's tube is made of rubber and has an internal diameter of 8 or 9 mm (sizes 8 or 9). Its lower end is bent at an angle of approximately 15°. (See Fig. 1.) On this bent portion of the tube

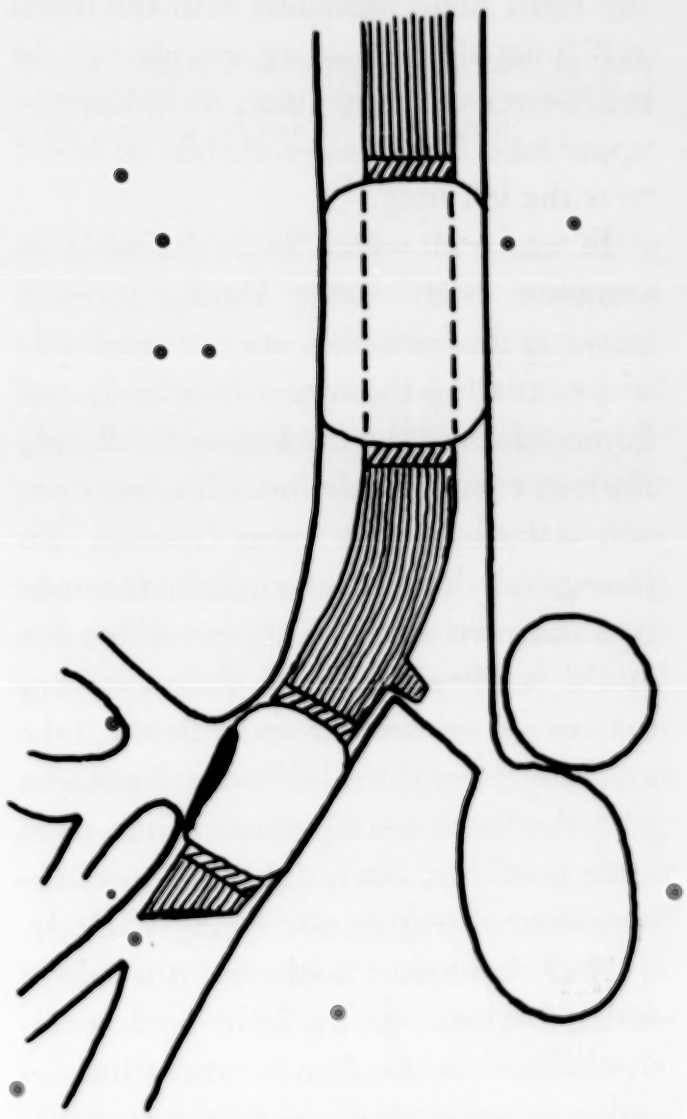


Fig. 1. Diagram of Green's tube in place for right lung anesthesia. Note the hole for ventilation of the right upper lobe.

TABLE 1. Preoperative lung volumes and airway dead space in five subjects.

(Bracketed figures = per cent of predicted values.)

Case	Sex	Age	Height cm	Weight kg	Lung volumes before operation, in liter (BTPS)				Airway dead space in ml (BTPS)				
									With tracheotomy		Without tracheotomy		Reduction %
					Vital cap. liter	Resid. cap. liter	Max vol. vent. l/min	FEV %[a]	Single determ.	*M*	Single determ.	*M*	
Sv.J.	M	53	187	94	3.5 (63)	1.91 (100)	69 (51)	—	67. 87, 61, 67, 64	69	160, 168, 195, 186, 195	180	62
B.F.	M	59	164	54	3.4 (92)	3.13 (180)	61 (56)	—	61, 70, 57, 43, 53	57	253, 257, 223, 253, 253, 246	247	77
Si.J.	M	66	171	73	3.9 (93)	—	99 (90)	65	84, 90, 80, 90, 100, 100	91	202, 211, 185, 194	198	54
B.W.	F	43	159	66	3.3 (100)	—	88 (98)	79	36, 46, 36 36, 23, 32 36	35	140. 122, 118, 127, 135, 144, 135	132	63
H.M.	F	37	172	66	4.1 (100)	1.52 (100)	55 (57)	—	25, 29, 39 18, 18	26	—	—	—

[a] FEV % = forced expiratory volume in first second as per cent of forced vital capacity.

The finding mentioned in the preceding section agrees well with the results obtained by Carter & Giuseffi (1951), who found that by tracheotomy in 3 cadavers the so-called anatomical dead space was reduced by 110, 115 and 125 ml respectively.

Blakemore (1953), using Fowler's method, found a reduction of "from 50 to more than 120 cc following tracheotomy". In our cases the reduction was found to be somewhat greater.

Consequently, from the viewpoint of respiratory economy, tracheotomy is to be highly recommended for cases with shallow breathing and difficult or trying respiratory work; and it is particularly appropriate when secretions in the air passages further impair breathing.

SUMMARY

The respiratory dead space (airway dead space) was determined by Fowler's method in 5 cases with tracheotomy, as well as in 4 cases after tracheotomy was closed. The dead space was reduced to about ½–⅓, and possibly even a greater reduction can be obtained by this means. Such a reduction is of great value from the viewpoint of the respiratory economy.

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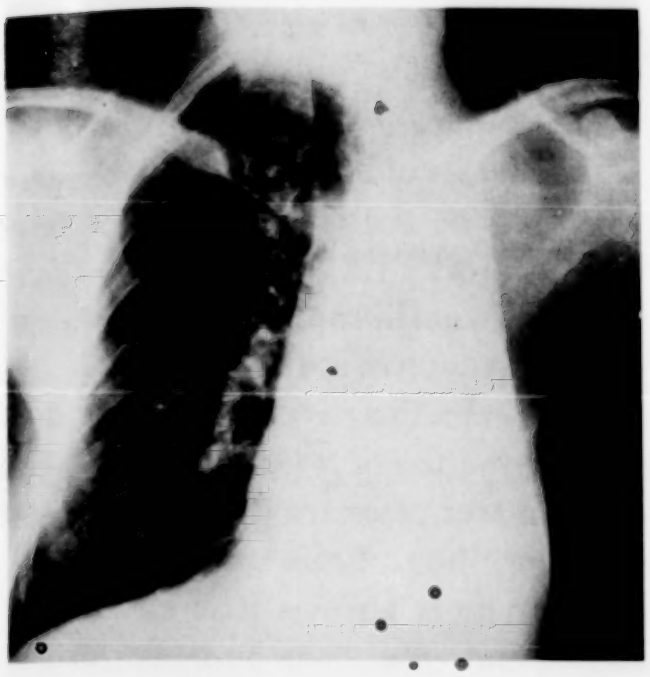


FIG. 2. Case 2. X-ray of the chest after left pneumonectomy with total thoracoplasty.

and scapula 3 times, viz. in 1955, 1956 and 1957 (Fig. 2). As the bronchial fistula to a empyema pocket remained (see Figs. 2 and 3), its extirpation was advised in 1958. The patient was placed in the face-down position with a Green's right endobronchial tube in place. After incision and extirpation of the remains of a peripheral empyema pocket between the chest wall and the aorta, the second empyema pocket with the bronchial connec-

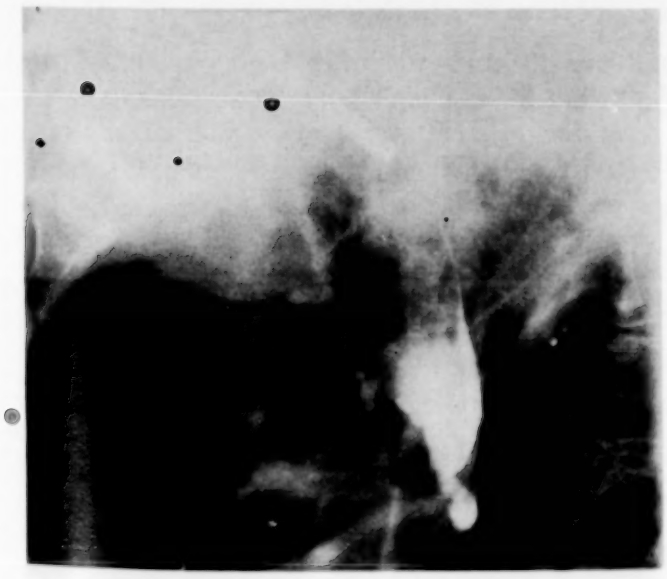


FIG. 3. Case 2. Bronchography demonstrating the fistula to a small residual empyema pocket.

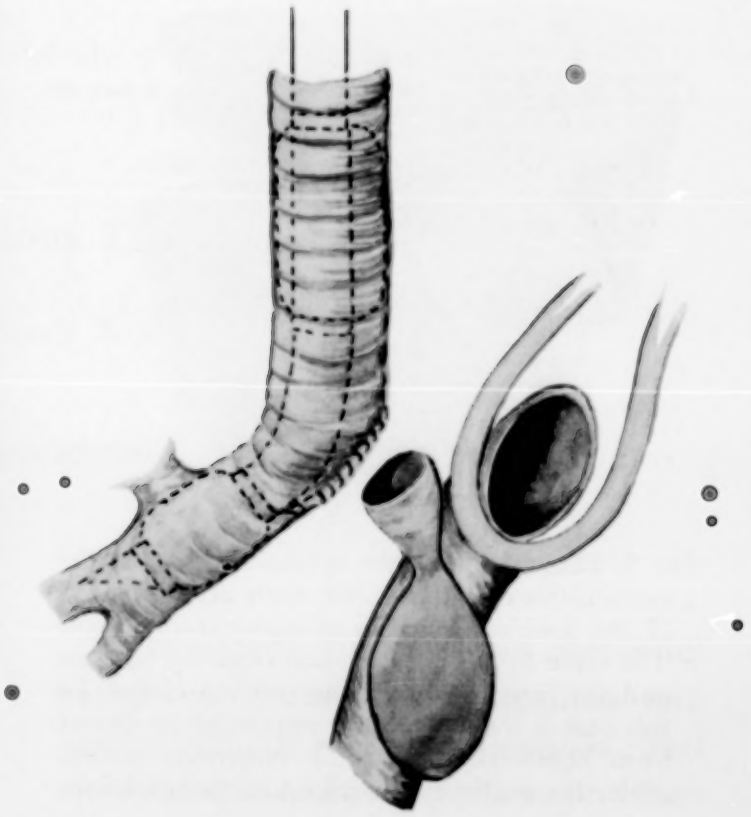


FIG. 4. Diagram showing Green's tube in place while the left main bronchus was excised from the trachea behind the aortic arch.

tion was dissected under the aortic arch. The peripheral part of that empyema was freed after a difficult dissection with an accidental opening of the stump of the pulmonary artery. As a follow-up to the trachea from below was not possible, the upper 3 pairs of intercostal arteries were divided and the arch of the aorta moved forward. The trachea and oesophagus could then be dissected behind the aorta. After dislocation forward of the aorta the remains of the left bronchus was excised from the trachea in healthy tissue. (See Figs. 4 and 5.) The opening to the trachea was sutured at ease with Green's tube in exact position. Then the central part of the empyema of the right main bronchus and aorta was dissected from behind and above the aorta until the plane of cleavage developed from below was reached. The remains of the

is a 2 cm long and 3 mm wide hole for the right upper lobe bronchus. An inflatable cuff is attached to the margin of this aperture. The tube has a second cuff for occlusion of the trachea. About one cm above the hole for the right upper lobe bronchus is a stiff rubber hook, similar to that on the Carlens' tube (Carlens, 1949). The tube is either introduced under direct vision through the larynx and pushed blindly down the trachea until the hook is felt to be engaged by the carina, or it may also be placed in the correct position with an introducing bronchoscope. When the bent portion of the tube lies correctly in the right main bronchus with the distal cuff inflated, respiratory sounds can be heard over the right lung, including the upper lobe. No sounds can then be heard over the left lung.

In cases in which it is desirable to ventilate both lungs during certain stages of an operation one can easily do so by inflating the upper (tracheal) cuff for occlusion of the trachea and deflating the lower (bronchial) one. This, however, will afford only a very narrow air passage to the left lung unless the tube is withdrawn until its lower orifice lies in the trachea. We have found it very easy to go up and down with the tube and only have it in the "down" position with the lower bent portion in the right main bronchus when right lung anesthesia is desired (e.g. in case No. 6, Table 1).

After induction with an ultra-short acting barbiturate we have used succinylcholine to facilitate intubation in order to avoid damage to the cords by the rubber hook. Anesthesia has been maintained with N_2O-O_2-*d*-Tubocurarin, the Engström respirator with intermittent over- and under-atmospheric pressure being used for the purpose (Björk *et al.*, 1956).

TABLE 1

Case no.	Age, years	Sex	Indication for use of Green's tube
1	69	M	High resection for left main bronchial carcinoma.
2	38	M	Left postpneumonectomy tuberculous empyema with bronchopleural fistula. See case report.
3	41	M	Left extrapleural pneumonectomy for destroyed lung with tuberculous empyema and bronchopleural fistula.
4	35	F	Re-resection for destroyed left tuberculous lung.
5	50	M	Extrapleural pneumonectomy for destroyed tuberculous left lung.
6	47	F	Stricture of left main bronchus. During operation left main bronchus found to be kinked. Left upper lobe + superior segment left lower lobe + osteoplastic thoracoplasty performed for pulmonary tuberculosis.
7	54	M	Destroyed left lung with tuberculous cavitation.

MATERIAL

Our material is summarized in Table 1. The advantage of the technique described is clearly illustrated by one of our cases.

Case 2: A 38-year-old man was treated with a left artificial pneumothorax from 1940 to 1945 for pulmonary tuberculosis. In 1950 an 8-rib thoracoplasty was performed and in 1952 a left pneumonectomy was carried out on account of a left main bronchus stenosis. A bronchopleuro-cutaneous fistula occurred, necessitating local resections of the chest wall

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Therapy in Bullous Emphysema

A Preliminary Report

STIG BJÖRKMAN

Bullous emphysema has in many cases a definite tendency to expand. The basic pathophysiological processes which cause this progress will not be discussed here. During clinical observation, however, it can be seen how the bullae gradually enlarge with simultaneously increasing compression of the adjacent pulmonary parenchyma, until one or more large, balloon-like distended emphysematous cysts are formed in one or both lungs.

Subjective symptoms appear only in the later stages of the disease. The prevalent symptom is dyspnoea, which in the early stages of the disease appears only with physical effort. However, as pulmonary changes progress, dyspnoea occurs more easily so that finally it occurs even at rest. In addition, the risk of a spontaneous pneumothorax due to a rupture of a bulla is not insignificant.

The therapeutic treatment considered in bullous emphysema has mainly been of a surgical nature. Extirpation of the lobe or the segment is performed if it is a solitary air cyst. In cases of multiple bullae, localized in more than one lobe, the local excision and plication-imbrication technique has been used.

It is outside the scope of this brief report to discuss the indications and contra-indications, complications and the final results of surgical therapy. However, the obvious fact that the contra-indications against surgical intervention are increased with the multiplicity and/or bilateral occurrence of the cysts should be pointed out.

It is evident that it would be desirable to have a therapeutic method which would permit destruction of the bullous changes in the lung without the hardships and inconveniences suffered by the patient as the result of an intra-thoracic surgical procedure. Such a possibility might result from injecting an astringent substance directly into the bullae, thereby obliterating their connecting airways. Once this occurs the enclosed gases are slowly absorbed, resulting in the disappearance of the cavity. Consequently the surrounding atelectasis will reinflate and the lung function improve.

Preliminary tests with such therapy have been carried on for some time. The following is only a short account of the first case with a sufficient period of observation after the treatment.

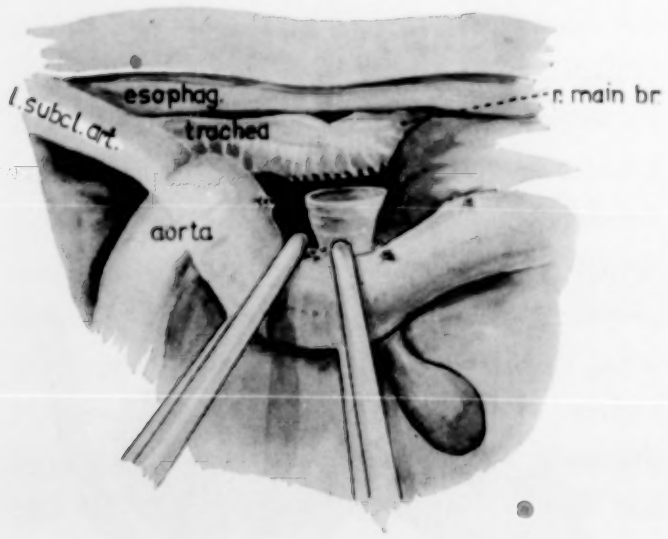


FIG. 5. Diagram from the operation showing the mobilization of the aortic arch after division of the four upper pairs of intercostal arteries. The main bronchus is excised from the trachea and the lateral hole in the trachea closed. In this case it was technically impossible to dissect from below the remaining empyema pocket under the aortic arch without its mobilization.

left bronchus in one block with the empyema pocket was then removed. This operation could not have been performed only from below the aorta. The patient made an uneventful recovery and left the hospital 17 days after surgery and is still 6 months later in an excellent condition.

DISCUSSION

In no cases have we encountered any difficulties with the positioning of the tube. With adequate ventilation the inflation pressure has never exceeded tolerable values. Suction through the tube has been very easy. There has been no case with laryngeal or tracheobronchial complications from the tube.

In all cases of left pneumonectomy we try to divide the bronchus at the level of the carina. This can easily be done below the aortic arch and by placing the catgut sutures as the bronchus is cut. In these cases there is no absolute indication for the use of a Green's tube, especially as wet cases are done in the face-down position. From our experience, however, it is obvious that all difficult surgery at the left bronchotracheal junction is considerably facilitated by the use of Green's tube, permitting right lung anesthesia.

SUMMARY

The right-sided endobronchial anesthesia with Green's tube is described and its advantages demonstrated.

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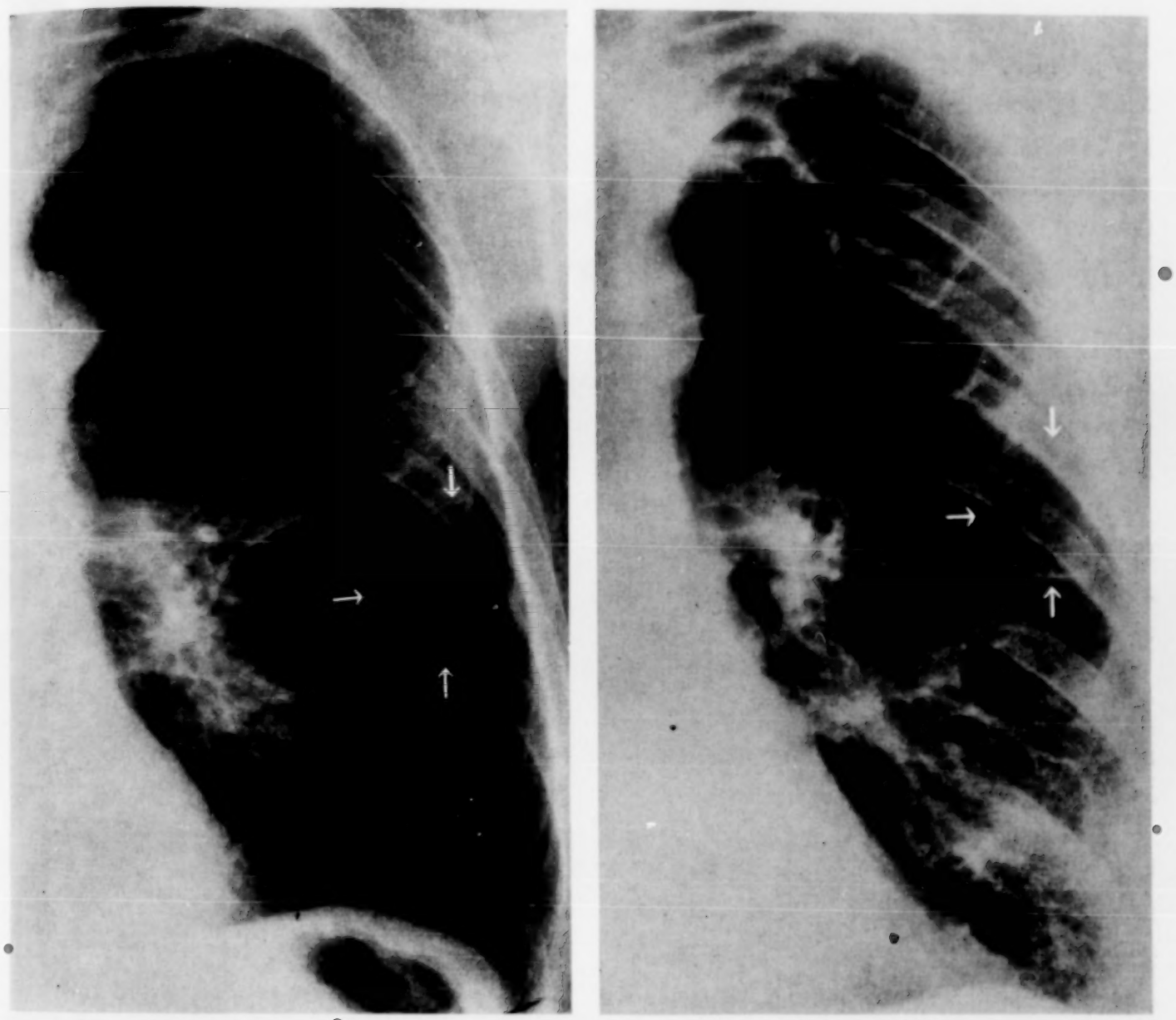


FIG. 1. Left lung before and five months after the treatment. Note, inter alia, the displacement of the hilar region and one of the lateral emphysematous bullae in the cranial direction on the occasion of the later examination.

After 3½ months, he was readmitted for a follow-up. He stated that he had considerably improved—so much that he had been in the woods a great deal and, in fact, a few days previously had walked 16 km in the forest without difficulty. He could go up three flights of stairs without too much trouble but did experience some shortness of breath on going up a hill. He still had an occasional hacking cough.

He had gained 3 kg in weight. The chest films showed a definite decrease of the bullous emphysema in the left upper lobe and a lessening of the compression of the left lower lobe caused by this emphysema. The left hilar region had returned to a higher and more normal position (Fig. 1). The residual capacity had decreased by 0.5 l and was now 2.28 l, the total capacity was 7.02 l, MBC had increased from 64 l/min. to 85 l/min. When testing the physical working capacity, the respiratory rate at

CASE REPORT

A 58-year-old lumber workman, former skiing competitor and used to heavy work was admitted to the medical thoracic clinic because of shortness of breath that had increased during the last 3 to 4 years. Five months prior to admission this dyspnoea forced him to quit work, gradually being so severe that he could hardly walk up one flight of stairs without resting. He had also a hacking cough, a sense of pressure across his chest on making any effort, and heart palpitations now and then.

Examination showed a man normal in build and with a not emphysematous chest configuration. The heart was without remark, both physiologically, electrocardiologically and roentgenologically. Roentgen examination showed widespread bullous emphysema in the lungs, mainly in the upper lobes but particularly on the left side. Both diaphragmatic arches were planed and showed reduced mobility. Residual capacity 2.78 l, total capacity 7.19 l. MBC 64 l/min. Two different tests of the physical working capacity on the cycle-ergometer gave similar results of an increased respiratory rate of 35/min. already at the level of 450 kg/min.

It has been shown that a deposit of aureomycin in the pleura space in spontaneous pneumothorax causes an aseptic inflammatory reaction, which may result in a desirable obliteration of the pleura leaves. This preparation was therefore chosen in an attempt to obliterate the airways leading to the largest bulla in the left upper lobe. This bulla was punctured percutaneously with a fine needle; 10 cc of physiologic NaCl containing 50 mg of aureomycin was then injected into the cavity. The patient did not feel any discomfort. The same procedure was repeated twice several days later with an increased dose and concentration of aureomycin, each time without the patient feeling any subjective inconvenience. No roentgenological changes appeared.

It was then decided that a change should be made to injection with a more effective astringent, and 2 % silver nitrate solution was chosen. To prevent coughing and thereby to lessen a possible caustic effect on the bigger bronchi, a small amount of the local anesthetic xylocaine was first injected into the bulla. To have the anesthetic reach all parts of the inner surface the patient was placed in a series of different positions. Then 2 ml of 2 % silver nitrate solution was injected and the patient again placed in various positions. This time there were complaints of pain at the injection site and some dyspnoea, which cleared shortly.

Chest X-rays taken the following day showed that small levels of liquid had appeared within several of the apically located bullae, which were surrounded by irregular infiltrations of the lung parenchyma. An insignificant pneumothorax could be seen. The latter reabsorbed in 3 days and the infiltrations disappeared after about 3 weeks. During these 3 weeks the bullae decreased in size, while the lower part of the left lung expanded upwards. The patient had a fever for 5 days, max. 39°C, after the injection. He then became afebrile, and within little more than one month after the injection he was discharged home in good condition.

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From Söderby Hospital, Uttran, Sweden

Complications of Internal Medical Importance after Surgical Treatment of Pulmonary Tuberculosis

T. Bruce, G. Dahlström and L.-G. Uggla

In close connection with operations for pulmonary tuberculosis a number of complications of an internal medical nature may arise. We have found it to be of interest to examine in this respect the material at Söderby Hospital. We have here excluded purely surgical complications, such as postoperative hemorrhages and states of shock, as well as bronchial fistulas and air leakage. Nor shall we discuss infections in wounds and apicolysis spaces which have required successive surgical decisions. Nor, in this connection, will reference be made to states of fever with mononucleosis-like blood pictures after operations for pulmonary tuberculosis which have been observed at the hospital and of which a preliminary account has been given earlier (Bergström & Dahlström, 1957).

Surgical treatment of pulmonary tuberculosis has been carried on at Söderby Hospital since 1930, but it was not until February 1954 that resections were performed. From February 1954 to and including August 1958 thoracoplasty has been performed in 134 and resection in 487 patients. Somewhat more than 600 patients have in all thus been operated upon. Our investigation is restricted to this period of time. The operations have been performed by surgeons from Crafoord's group.

The complications we shall discuss in this paper are, in the first place, ventilatory insufficiency and, further, cardiological and neurological disturbances (Table 1).

The material is not suitable for a frequency study, as the cases in which the operative risk has been deemed particularly high have been treated at the Sabbatsberg Hospital. During the period in question, however, also the Söderby material has included a considerable element of "bad risks".

Table 1.

1. Ventilatory insufficiency
2. Cardio-vascular complications
(*a*) Pulmonary embolism
(*b*) Disturbances of rhythm and conduction
(*c*) Pericarditis
3. Neurological complications
(*a*) Lesion of cervical plexus (contralat. side)
(*b*) Lesion of N. thoracal. long. (wing scapula)
(*c*) Other complications

VENTILATORY INSUFFICIENCY

Among the complications which are of particular interest from the viewpoint

450 kg/min. had decreased from 35/min. to 23/min. and at 600 kg/min. it was only 25/min.

The pulmonary function has thus improved both subjectively and objectively.

DISCUSSION

It is too early to decide which preparation may prove most suitable for use as an astringent in local treatment of bullous emphysema. Experiments with substances other than silver nitrate are being continued. If this method should prove to have the value expected, it might perhaps be possible to treat a group of cases which so far has been unsuitable for therapy.

SUMMARY

A method for bloodless local treatment of bullous emphysema with multiple foci is illustrated by the first case, where a sufficiently long period of observation has passed. By injecting directly into the bullae a 2 % silver nitrate solution, shrinkage of the bullae was obtained. Five months after the intervention the patient had both subjectively and objectively a definitely improved pulmonary function.

TABLE 2.

Types of operation	No. of cases
Thoracoplasty, 3–5 ribs	3
Resections	
Segmental resection in one lobe + "roof thoracoplasty"	1
Segmental resection in two lobes + "roof thoracoplasty"	1
Lobectomy + "roof thoracoplasty"	6
Lobectomy + segmental resection + "roof thoracoplasty"	1
Pneumonectomy + thoracoplasty	3
Total	15

tomy plus segmental resection in one case. In all these cases at the same time a "roof thoracoplasty" had been performed. Pneumonectomy with simultaneous thoracoplasty had been performed on three patients (Table 2).

The ventilatory insufficiency developed at varying rates, but all patients were strongly affected when the tracheotomy was carried out. In two cases the procedure was performed on the same day as the operation, in seven cases the day after. Three patients were tracheotomized after two days, two patients after four and one, finally, sixteen days after the operation.

In three patients it was not necessary to have recourse to respirator treatment. One patient died before it was possible to establish effective artificial respiration through the tracheostoma. In the remaining eleven the Engström respirator was connected to the trachestomal cannula. The period of time during which this treatment was continued varied from two to seventeen days (Fig. 1).

As regards postoperative roentgenological changes, the following may be stated.

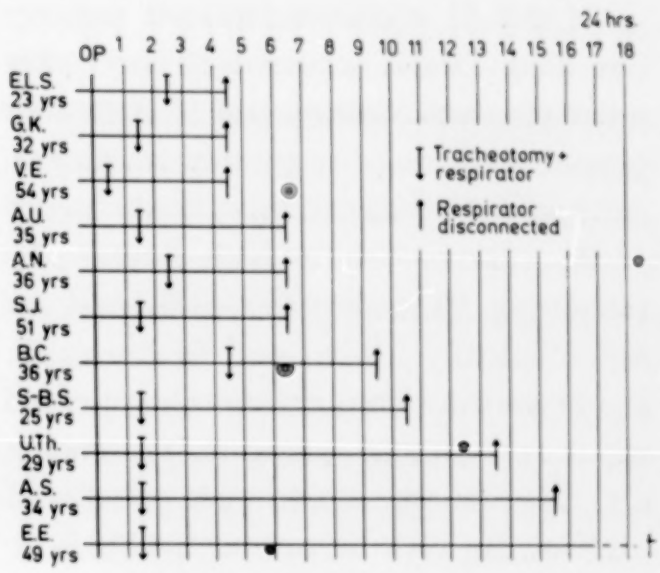


FIG. 1.

In nine cases, simultaneously with the development of the ventilatory insufficiency, patchy consolidations were shown roentgenologically, corresponding to stagnation of secretion or bronchopneumonia. Such changes were found only on the non-operated side in five patients, of whom one also had total atelectasis in the operated lung. In four cases there were bilateral changes on the X-ray.

Total atelectasis on the operative side was present in another case. Poor air-content in the operated lung, though without distinctly deliminated consolidations, was observed in two other patients.

In one case, after pneumonectomy, there was a marked displacement of the mediastinum with compression of the remaining lung. The displacement was due to a considerable hemorrhage on the operated side; despite evacuation of the blood, the ventilatory trouble remained. Compression with atelectasis of the lung was observed in two patients after thoracoplasty. The compression was due to hemorrhage and paresis of the diaphragm in one of these cases and to haemo-pneumothorax in the other.

of internal medicine, ventilatory insufficiency occupies the first place.

In 15 patients—eight men and seven women—there have arisen in the period in question ventilatory insufficiencies of such a serious nature that it has been deemed necessary in the postoperative course to perform tracheotomy and eventually to give respirator treatment. We have not included in this group those cases that were already so affected during the operation that tracheotomy was carried out as a last step in the operation.

The age of the 15 patients has varied from 23 to 61 years.

Two patients were *sputum positive* within the two months preceding the operation, the rest were abacillary, but one of them had copious expectoration.

The *investigation of lung function* before the operation in these 15 cases showed that the ventilation, assessed as *maximal breathing capacity* in liters/min., was in only two cases considerably, and in three cases moderately, reduced. Ten patients had an only slightly reduced or completely normal ventilation.

The *residual quotient* was in three patients moderately and in one case considerably increased; all of these had also distinctly reduced ventilatory capacity. *Bronchospirometry* had been performed in 10 cases. Only in four of these was the lung which was to be operated upon bronchospirometrically decidedly the better one. In the remaining five the operation was to be performed on the definitely inferior lung, and bronchospirometry had therefore not been considered necessary.

In three cases the preoperative *ECG examination* showed right preponderance without other pathological changes. One patient had negative T_1 without other pathological signs; in the others the ECG findings were normal.

Heart catheterization was carried out in two cases. In one of these there was a pathological rise in pressure in connection with work and occlusion of the pulmonary artery to the lung that was to be operated upon. In the other case pressures were normal both during work and during occlusion; on the other hand there was a slight lowering of P_{O_2} in connection with the occlusion at rest and during work.

As we always carry out preoperative heart catheterization if pulmonary hypertension is suspected, both the fact that the examination was performed on only two patients and the short account of other function studies go to show that ventilatory insufficiency had arisen in persons who had primarily not been considered particularly "bad risks". The physiological examinations scarcely afford the possibility of sorting out the patients who run the risk of developing ventilatory insufficiency. The complication thus appears very capriciously. Just as we have met with ventilatory insufficiency where we had not expected difficulties, so, too, in many cases with poor breathing capacity and even signs of strain on the right heart we have had an uneventful postoperative course.

The following types of operation were represented: thoracoplasty involving three or five ribs had been performed on three patients; segmental resection in one lobe and segmental resections in several lobes had each been carried out in one case; lobectomy in six cases and lobec-

and to increase the ventilation, and they have become mentally confused and apathetic. On the other hand, not even careful control of pulse and blood pressure has afforded any diagnostic help worth mentioning. Such a case is illustrated in Fig. 3.

The alkali reserve has been followed in a number of cases without appreciable changes being observed, which is in agreement, moreover, with experience from polio care.

We had not yet, when the ventilatory insufficiencies occurred, the possibility of carrying out analyses of oxygen and carbon-dioxide tension in the blood. Such analyses are of great importance both for the diagnosis and for following the effect of treatment, but they can scarcely be used as daily routine in all operated cases. Such laboratory tests can never take the place of careful bed-side supervision that can be carried out by trained staff accustomed to observe, judge and report changes in the patients' general condition and way of reacting. That the general clinical observations are of great importance emerges also from the fact that even by utilizing advanced functional investigations it has not been possible to foresee which patients have run a special risk of developing ventilatory insufficiency. It may be worth while pointing out that resection and thoracoplasty have been performed at the same stage in all the resected patients suffering from ventilatory insufficiency. It can scarcely be proven that the combination of resection with simultaneous thoracoplasty has contributed to the occurrence of the ventilatory insufficiency, even if this combination undeniably implies an added strain for the patient.

Different causes have doubtless contributed to the occurrence of our ventilatory insufficiencies. Great importance must in almost all the cases be ascribed to stagnation of secretion due to the difficulty of coughing up matter, either on account of unsatisfactory technique or lack of the will to cooperate or because of paresis of the diaphragm of a more or less transient nature. The preoperative and postoperative physiotherapy is here of great importance, and in the course of the years we have come to attach considerable importance to this part of the treatment. A purely muscular exhaustion may also often have been a contributory factor. The significance of this factor becomes obvious when one considers that the energy required for quiet breathing at rest is estimated to be about 0.5 kgM/min., but rises to several hundred kgM/min. for maximal respiration (Comroe *et al.*, 1955). Since one knows that these patients have as a rule a low physical working capacity, it is understandable that the respiration may fail through sheer exhaustion.

CARDIO-VASCULAR COMBLICATIONS

Cardiac and vascular complications have occurred surprisingly rarely. We have observed only one pulmonary embolism; this proved fatal. The cardiac complications have otherwise been constituted by *disturbances of rhythm and conduction* and by *pericarditis*.

We have in some cases recorded transient fibrillation. In one patient

Of the 11 respirator-treated patients one died. Death occurred 18 days after a five-rib thoracoplasty and 17 days after commencement of respirator treatment. Autopsy revealed extensive fresh spread of the tuberculosis in both lungs. The remaining 10 recovered rapidly and are now clinically healed and fit for work. In one person a tracheal stenosis appeared which necessitated operation. The results are thus on the whole very good and confirm the view advanced by Björk & Engström in 1957 concerning the favourable effect of the respirator treatment after pulmonary operations.

Of the three patients who were not connected to the respirator, two managed well with a clearing of the respiratory passages by suction through the tracheostomal aperture and the relief for the ventilation thereby implied. The third patient died suddenly of a big hemorrhage within the operative region.

In recent years, not least in connection with polio care, the clinical picture in cases of respiratory acidosis has become well known (compare e.g. Ström and coworkers, 1956). There is every reason to suspect that the symptoms occurring in the cases of ventilatory insufficiency described by us were caused partly by such respiratory acidosis with accumulation of carbon dioxide in the blood. Deficient oxygenation may also have played a role, and an over-exertion of especially the right ventricle of the heart in consequence of increased resistance in the pulmonary circulation may also have contributed.

Classical signs of respiratory acidosis are said to be increase of blood pressure, tachycardia, mental confusion and, finally, coma.

It is of interest to ascertain whether these symptoms have also been present in our cases, where the ventilatory insufficiency was not, as in polio, caused by muscle paresis and damage of the respiratory centre, but by reduction of functioning parenchyma, uneven ventilation of the lungs etc.

A closer study of the material shows that only a few cases manifested symptoms coinciding with the characteristic picture of the disease. Such a case is illustrated in Fig. 2.

In the majority of our patients, however, the treatment was started on the basis of the general clinical observations. The patients have seemed tired out and unable to cooperate in the physiotherapy intended to promote the coughing up

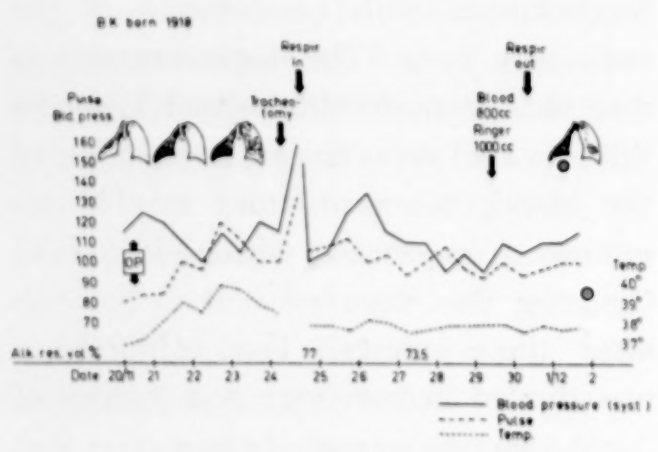


FIG. 2.

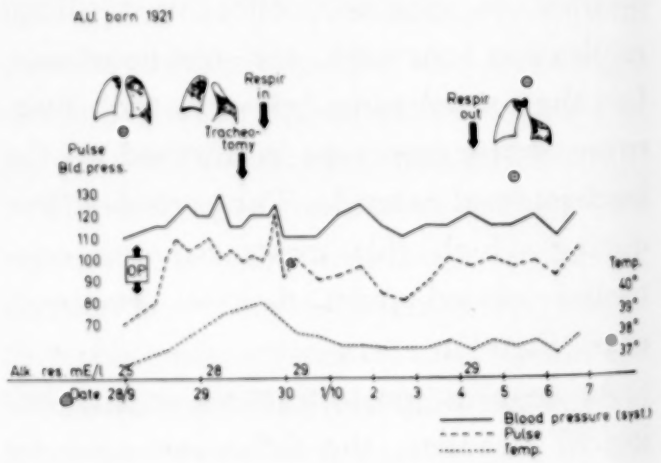


FIG. 3.

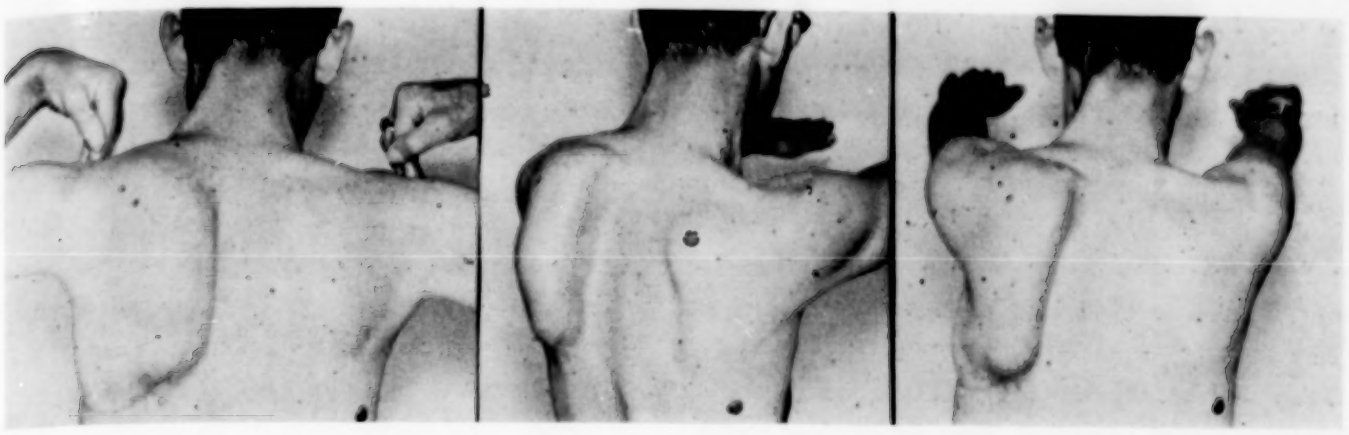


FIG. 4.

classical picture of paralysis of M. serratus anterior caused by an adverse effect upon N. thoracalis longus. With both cases a good result was obtained with special gymnastic treatment.

In one case the neurological complication was of a more unique character. Resection of a segment in each of the superior and inferior lobes in the left lung, with "roof thoracoplasty", was performed on a 32-year-old man. Immediately after the operation there were signs of paresis of N. recurrens with hoarseness. There was also difficulty in manoeuvring the tongue, which deviated to the left. After a couple of weeks there was distinct left-sided atrophy of the musculature of the tongue. There was also a reduction of sensibility behind the right ear, corresponding to the distribution area for the first cervical nerve. The consulting neurologist was of the opinion that the symptoms must be referred to a central lesion. It has not been possible to elucidate the cause. It was possibly a matter of an embolism.

We have now discussed some complications of an internal medical nature which occurred early or relatively early in the postoperative course. Complications that may occur later are bronchectasias arising in consequence of retention of secretion, and atelectases persisting for a longer period. Sequelae of this kind are not generally manifest until after the lapse of several months. Postoperatively occurring pulmonary hypertension with development of cor pulmonale chronicum is also a long-range problem, and falls outside the scope of this account.

One runs the risk of getting a pessimistic view of the value of a method of treatment when occupying oneself with the complications. As regards surgery in pulmonary tuberculosis the pessimism is in a high degree uncalled for. As a matter of fact, complications are surprisingly few when seen in relation to the magnitude of the operations and the gain entailed. Lung surgery has indeed a great share in the success that the treatment of tuberculosis has had during the last few decades.

SUMMARY

The material consists of about 600 patients at Söderby Hospital who were operated on with thoracoplasty or resection during the period

who before the operation had manifested intraventricular conduction disturbance there occurred in connection with the operation a right-sided bundle branch block. In a man of 50 years with earlier slight signs of cardiosclerosis there occurred postoperatively frequent ectopic beats from different foci; the rhythm became regular after digitalis and quinidine medication.

Many of the operated patients were over 50 years of age. As the indications for the operations are further extended and come to cover an increasing number of persons in the higher age-groups the risk of cardiac complications here described will be increased. The importance, in doubtful cases and with older people, of carrying out a detailed preliminary examination of the circulatory organs, including, *inter alia*, the ECG during work, is obvious.

Quite another type of cardiological complication is pericarditis. During the period covered by the investigation we have observed two such cases, both after left-sided pleural-pneumonectomy. The postoperative course was at first relatively normal, and the fever subsided in the usual way. After a period of 6–8 weeks the temperature began to rise again and there were also precordial pains and palpitations. In the one patient a marked increase of the heart volume was roentgenologically observed. In the other case no enlargement of the heart could be established, but here there were typical pericardial friction sounds. Both had also electrocardiographic changes of the type occurring in pericarditis.

The course of the healing was favourable. The temperature was normalized in 2–4 weeks. The pathological electrocardiographic findings disappeared. The patients have been observed for more than 2 years without any signs of circulatory disturbance, e.g. in the form of constrictive pericarditis, appearing.

It has in these cases not been possible to decide whether the pericarditis has been due to non-specific inflammation or exacerbation of the specific process. Probably it has been a matter of an activation of the tuberculosis.

NEUROLOGICAL COMPLICATIONS

In four cases, some weeks after the operation, there appeared symptoms indicating lesion of the cervical plexus on the non-operated side. The patients manifested on that side atrophy of M. trapezius and M. supraspinatus, weakness in the shoulder joints and difficulty in lifting the arm above the horizontal plane. The lesion was only observed when the active gymnastic exercises had been commenced. The atrophy was in one case very strongly pronounced, but within a year there was almost complete restitution. In the other three cases the atrophy was moderate or slight, and the symptoms of rather short duration. It seems likely that this type of paralysis arose as a consequence of the nerve plexus being exposed, owing to the patient's position, to pressure during the operation.

Two patients, men of 46 and 53 years of age, both of whom had been operated upon with resection and decortication with thoracoplasties, manifested after 2–3 months a typical wing scapula on the operated side (Fig. 4), in all respects a

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Teflon Prosthesis in Tracheal Defects in Man

S. Ekeström and E. Carlens

Extensive experimental work has shown that in many respects teflon appears to be the most suitable prosthetic material in both vascular surgery and surgery of the respiratory passages. It is easy to shape and sterilize and it has good tensile strength which is very little affected by the body fluids; it has, moreover, and above all, in a higher degree than any other inorganic material hitherto tried, the quality of "tissue friendliness" (Harrison, Swanson & Lincoln, 1957; Le Veen & Barberio, 1949; Ekeström, 1958). It was therefore considered only natural to try some form of teflon prosthesis in major tracheal defects also in man. In connection with experimental investigations in 1958 Ekeström gave a preliminary account of reconstructions after extensive tubular resections of the intrathoracic trachea in 3 patients. Two were unsuccessful, but one of them was at that time still alive and in a relatively good condition 5 months after the operation. As a further 15 months have now elapsed since the operation, we shall present a more detailed report of the case. First of all, however, we should like to give a brief account of the reconstruction of a large window defect in the upper part of the trachea in another patient.

Case 1.—S. S. 25-year-old married woman On 19.2.57 right-sided pneumonectomy with simultaneous wall-plastics for tuberculosis. The day after the operation pronounced respiratory insufficiency. Tracheotomy was accordingly performed and the patient was treated with respirator for a rather long period. On several occasions there were difficulties with the cannula and troublesome exchanges of cannula. After removal of the cannula there developed after a couple of months a 3 cm long, complete stricture of the trachea 3 cm below the larynx. Tuberculous etiology could not be entirely eliminated. Dilatation treatment was tried without effect. On 31.7.57 the strictured region was resected and replaced with a steel-wire-supported skin graft ad modum Gebauer 3 cm in length. For the first month satisfactory respiration, but then the wire began to appear in the lumen and copious granulation necessitated bronchoscopy every two weeks. On 5.5.58 fresh operation. After an incision in the median line the wire was removed. For a good 3 cm the tracheal wall was found to be completely soft within almost the whole circumference. To prevent collapse, a 5 cm long and 1 mm thick teflon tube with an inner diameter of 10 mm was inserted as shown in the figure. The rim was slightly bent outward at the ends to prevent any gliding. It was not possible to close the trachea completely about the middle of the prothesis. The defect was covered with soft parts and the skin primarily closed. The postoperative period was quite free of complications, with only slight coughing irritation for the first few days. No coughing after this. No signs of stridor. Now, 12 months after the operation, normally active as housewife. (Fig. 1.)

February 1954 to August 1958. The complications noted in the first place are ventilatory insufficiency and cardiological and neurological disturbances. Sequelae arising late in the post-operative period are not discussed.

Ventilatory insufficiency of such a serious nature that it was necessary to resort to tracheotomy and respirator treatment occurred in altogether 15 cases and appeared after both thoracoplasty and resection. The complication occurred capriciously, being observed also in persons who against the background of good functional tests had not primarily been considered "bad risks". The cause of ventilatory insufficiency was chiefly retention of secretion and difficulty in clearing the bronchial tree, but also exhaustion. Characteristic signs of respiratory acidosis are stated to be rise in blood pressure, tachycardia, mental confusion and finally coma. Even if these symptoms existed in a few cases, the rise in blood pressure and pulse was not observed in the majority. Decisive importance must be ascribed to the general clinical observations and the careful supervision at the bedside by experienced staff trained to observe, judge and report changes in the patients' general condition and way of reacting. In the majority tracheotomy and respirator treatment had to be established on the second or third day after the operation. Only one patient died; autopsy revealed extensive fresh spread of the tuberculosis in both lungs.

Cardiac and vascular complications were, besides pulmonary embolism in one case with fatal issue, disturbances of rhythm and conduction and pericarditis. The disturbances of rhythm and conduction—fibrillation and frequent ectopic beats—were found chiefly in older patients in whom unequivocal signs of cardiosclerosis had sometimes been shown before the operation. It was possible to cope successfully with these cardiac complications, and there were no deaths. As the indications for operation are extended to include more persons in the higher age-groups the risk of complications of this kind is increased. Pericarditis was shown only after left-sided pleural pneumonectomy. Both roentgenologically demonstrable enlargement of the heart, pericardiac friction sounds, and typical electrocardiographic changes occurred when the pericarditis had developed 6 to 8 weeks after operation. The course of healing was favourable.

Neurological complications were paralysis of M. serratus anterior with typical wing scapula on the operated side, caused by an adverse effect upon nervus throacalis longus, as well as lesion of plexus cervicalis on the non-operated side with atrophy of M. trapezius and M. supraspinatus, weakness in the shoulder joints and difficulty in lifting the arm above the horizontal plane. This type of paralysis was probably caused by the nerve plexus being exposed to pressure owing to the patient's position during the operation. In all cases good therapeutic results were obtained with special gymnastics.

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the tube. The granulation tissue consisted of loosely attached polypoid formations constituting a loose, edematous, cell-rich granulation tissue which was relatively abundantly infiltrated with plasma cells, lymphocytes and, to a lesser extent, leucocytes. In the anastomotic area this granulation tissue was partly covered with laminated squamous epithelium with moderate degenerative changes. As soon as the granulation tissue was removed, the respiratory trouble was relieved. It was subsequently necessary to carry out such bronchoscopic clearings at intervals of 2–3 weeks. Gradually the loose bundles of granulation tissue disappeared and were replaced in the upper anastomosis by a thin membarne of a relatively firm, connective tissue type, and the lower anastomosis was in the sequel wider and without granulations. The connective tissue membrane in the upper anastomosis necessitated dilatation about every third week. In order to prevent the development of a stricturing connective tissue membrane in this anastomosis, a teflon tube shaped like a cotton-reel, 2.5 cm in length and with a diameter of 12.5 mm was inserted on 17.9.57. The tube was so placed that half of it came to lie inside the upper part of the healed-in plastic prothesis, and it thus came to cover the anastomotic area. The insertion was made through renewed tracheotomy. After a short time the tracheostoma closed and the patient was discharged without subjective inconvenience. She has since been, and 8 months after the insertion of the teflon tube still is, perfectly comfortable and in a good general condition.

DISCUSSION

In the first case a teflon tube placed in the cervical trachea was able for 12 months to prevent a collapse in an area about 3 cm in length, where a resection of a completely strictured part had been performed. The tube obviously did not cause any trouble. The patient did not manifest any signs of the formation of granulation tissue at the upper and lower ends of the tube, probably owing to the fact that the tube was held in place by tight-fitting connective tissue round the middle part of the teflon tube, whereas, on the other hand, the upper and lower ends of the tube projected into normal trachea, which was wider than the outer diameter of the tube, so that the latter did not there give rise to any trauma in the tracheal wall worth mentioning. The second case refers to a 54-year-old woman who is still alive 1½ years after a tubular resection of a 5 cm long portion of the intrathoracic trachea. There is as far as we are aware only one other case described in the literature in which a patient has survived a tubular resection with reconstruction of the intrathoracic trachea. This was a patient described by Carlens & Wiklund (1956) with a stenosing cylindromatous tumour in the lower half of the trachea, where in 1952 Crafoord performed a tubular resection of the intrathoracic trachea and a reconstruction with a tantalum net covered with fascia lata. As is frequently the case when a net of tantalum or stainless steel is used, there was also here a rich ingrowth of granulation tissue through the net, narrowing the lumen in the whole of the reconstructed area. It was therefore necessary to remove the tantalum net by another thoracotomy. This patient is still alive 7 years after the tubular resection. She has a prolonged tracheal cannula which reaches from the fossa jugularis down to the carina. The cannula is exchanged and cleaned at intervals of some months. The patient is back to normal work.

Both experimental and clinical investigations have shown that a connective tissue membrane is developed especially at the site of the upper anastomosis



FIG. 1. The teflon tube inserted in the cervical trachea. Within this region the patient has a stricture after tracheotomy. The inner tube has now been lying in position for 12 months without occasioning any discomfort.



FIG. 2. From case 2: The reconstruction with teflon-reinforced connective tissue tube may be seen between the two arrows. At the upper arrow was developed a membranous stricture, and one sees the inserted inner tube which now covers the upper anastomosis and prevents fresh outgrowth of stricturing connective tissue.

Case 2.—S. E. 54-year-old woman. In 1956 a cylindromatous tracheal tumour was discovered, which had then been giving trouble in the form of a tickling cough and infection of the upper respiratory passages for about 1 year. The tumour was located in the trachea approximately 3 cm above the carina. It was repeatedly coagulated through a bronchoscope from January 1956. Recidivation after every coagulation. On 1.8.57 a teflon prothesis was inserted in the abdominal wall, and on 9.9.57 a tubular tracheal resection was performed, followed by reconstruction with a plastic-reinforced connective tissue tube that had been formed in the abdominal wall according to an experimentally worked out method (Ekeström, 1958). By the time for the operation the tumour had grown round the whole trachea within an area about 5 cm in length, and in its lowest part it reached to approximately 1 cm above the carina; both nervi recurrentes could be dissected out and saved. Tracheotomy was performed immediately after the operation. The course of the postoperative period was at first on the whole free of complications. Bronchoscopy a short time after the operation showed that the prothesis lay in a good position. In the sequel the patient had respiratory difficulties, as granulation tissue grew out a partial occlusion of the lumen, at first in both the upper and lower anastomoses and on one occasion also about in the middle of

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between the trachea and a sewn-in prothesis; this membrane gives rise to a progressive stricture. A short inner tube of teflon like that shown in Fig. 3

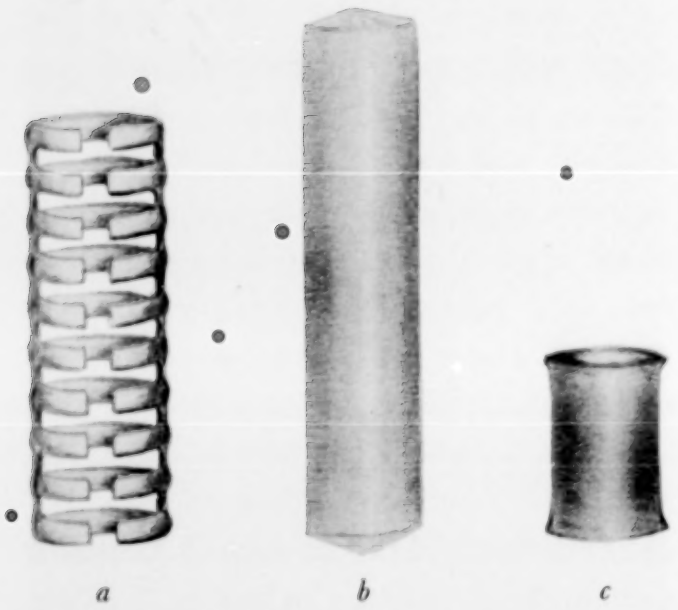


FIG. 3. (*a*) The teflon ring tube used to reinforce the rectus fascia when a tube is created in the abdominal wall; (*b*) around the solid tube is wrapped the rectus fascia, after which the teflon ring tube (*a*) is pushed over to form a sheath; (*c*) inner tube now used to prevent stricturing in cases 1 and 2.

can prevent the formation of a stricturing connective tissue membrane. The inner tube may be put in place in connection with the reconstructions performed in the experiments mentioned earlier or else, as in case 2, be inserted at a later stage. In the experimental reconstructions the inner tube has in isolated cases slipped out of position, and has sometimes probably not been necessary, and especially not in the lower anastomosis, where according to our experience rarely stenosis develops. Thus in case 2 there was in the lower anastomosis only a relatively moderate granulation in the form of polypoid formations. These granulations have shown but little tendency to reform after being removed via the bronchoscope.

With its relative friendliness to tissue, its physical properties, such as its high melting point (260°C), and its chemical inertness, teflon has proved very suitable as a supporting material in tissues. Teflon is also non-wettable. Le Veen *et al.*, who studied in different plastics the tendency to cause foreign-body reaction, found that besides giving rise to a very slight foreign-body reaction, teflon was also distinguished from other plastics by having a surface free from adsorbed protein. We have had similar experience as regards teflon and secretion from the respiratory passages, for it is only to a relatively slight extent that the secretion has stuck to the spot, and it has not dried fast in the form of obturating crusts on the inner surfaces of the tubes. The teflon tube should be so shaped as to prevent slipping, but it also seems to be of importance that the width be rightly adapted and the ends so rounded off that unnecessary irritation of the tracheal mucous membrane is avoided.

SUMMARY

Two cases of tracheal reconstruction are described. In the one a 5 cm long teflon tube has been inserted on account of complete stricturing of the cervical trachea. The patient is completely free of inconvenience after 12 months. In the second case a 5 cm long tubular resection in the intrathoracic trachea has been replaced with a graft containing a teflon skeleton according to a method described earlier. On a second operation a short teflon tube was inserted in the upper anastomosis to prevent stricturing. This patient is almost entirely free of discomfort 1½ years after the operation.

cough". Laënnec assumes that they are caused by a bronchitis which weakens the bronchial wall and produces secretions which stagnate and dilate the bronchi by pressure.

Corrigan in Dublin in 1838 suggested another factor which can produce bronchiectasis. While Laënnec and, after him, other French and English authors only talked about the changes in the bronchial wall as the reason for the development of bronchiectasis, Corrigan maintained that changes in the lung parenchyma are of great importance. He was of the opinion that chronical shrinking processes in the lung tissue dilate the bronchi by traction, and at the same time pull the chest wall inwards. He called it "cirrhosis pulmonum". Fig. 2 shows the lung from a boy who suffered from a badly drained empyema, which gradually produced a condition which closely resembles Corrigan's description of the cirrhosis of the lung.

Congenital cystic disease of the lung was first described by Thomas Bartholin in 1651,[1] later by H. Meyer in Zürich in 1859, by Barlow in 1879 and Grawitz in 1880. This origin of bronchiectasis and cystic disease has specially been stressed by German authors (Gravitz, Virchow, Biermer, Herxheimer), and also found a strong supporter in Sauerbruch (1934) who maintained that more than 80 % were congenital. English and American authors, however, maintained that congenital bronchiectasis is rare, and there is no doubt that bronchiectasis in children who have died immediately or shortly after birth is very rare—much too rare to account for all the cases of bronchiectasis in children and young people. To explain these we must look at the pre- and postnatal development of the lung.

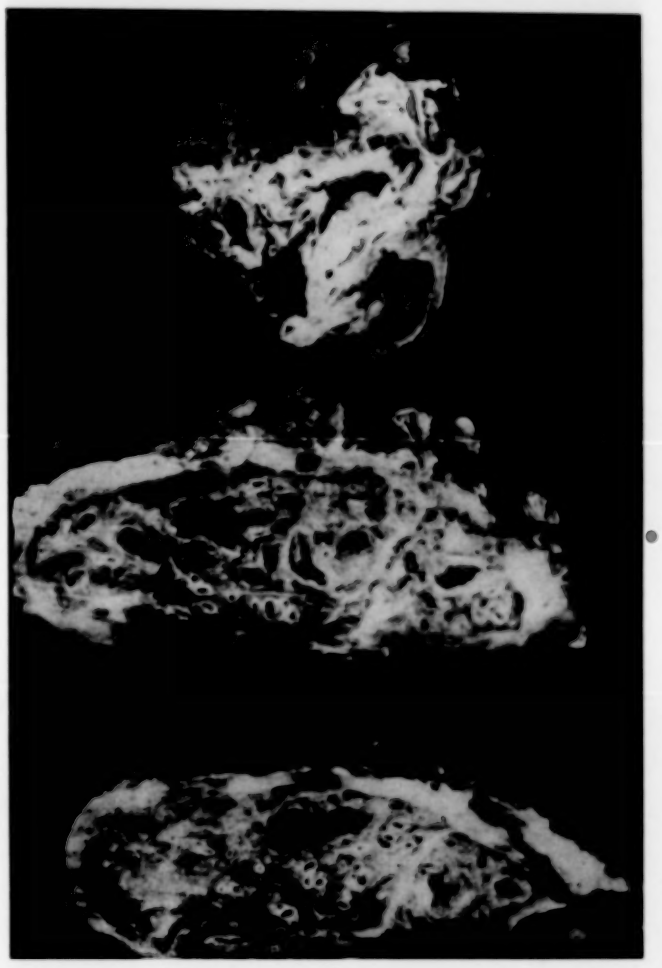


FIG. 2. Sections of the lung from a 10-year-old child which suffered from a badly treated empyema. A cirrhosis of the lung developed, which corresponds exactly to the description by Corrigan.

PRE- AND POSTNATAL DEVELOPMENT OF THE LUNG

The classical conception of the development of the lung, as described by Koelliker and His, was that the lung of mammals was fully developed at birth.

[1] Thomas Bartholin writes that Nicolaus Fontanus in a letter to Bartholin describes a child that died from marasmus at the age of 4 years. The autopsy revealed that the one lung was a single cyst.

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ACTA CHIRURGICA SCANDINAVICA. SUPPL. 245: 76–84, 1959

From Rigshospitalet, Copenhagen, Denmark

Bronchiectasis

Etiology, Surgical Treatment, and Prevention

E. HUSFELDT

Bronchiectasis seems to have been unknown both to the anatomists and the clinicians until Laënnec gave his classical description of the pathology, the clinical signs and the course of the disease in the first edition of his *Traité de l'auscultation médiate* in 1819. Laënnec (1819) tells how in 1808 a young medical student by the name of Cayol, who later on became Professor of Medicine, asked him to examine a lung, which the student had never seen described in the books. These were the lungs of a 3½-year-old boy, who for 3 months had suffered from whooping cough and then had been admitted to the Children's Hospital in Paris on January 30, 1808. At hourly intervals he brought up streams of foetid sputum. He died after a fortnight's stay in the hospital. The autopsy showed that the left lower lobe was heavy, and of a violet colour. When a cut was made through the lobe 1½ ounces of foetid, puriform liquid poured out. This liquid was contained in a multitude of round, smooth cavities lying close to each other, often communicating or else separated by thin walls. They all ended in the bronchial tree, and evidently were a continuation of this. (Fig. 1 shows a section of a lobe which exactly corresponds to Laënnec's description.)

During the following years Laënnec collected a considerable number of cases, and in the second edition of his *Traité*, 1826, he wrote that dilatation of the bronchi, without being common, was certainly not so rare as he used to think. "They are very commonly found in children, who have had whooping



FIG. 1. Section of the left lower lobe of the lung from a 15-year-old child which had suffered from chronic bronchitis from early childhood. The specimen corresponds exactly to the description by Laënnec.

lowing whooping cough, measles, influenza etc. or even aspiration during delivery has in later years been considered as the main reason for the development of bronchiectasis, especially by American and English authors. If a lobar bronchus becomes obturated by tough secretions, all air in the lobe will be quickly absorbed by the circulating blood in the lobe, and the lobe becomes atelectatic. The bronchi cannot be emptied by coughing, and will be filled by stagnating secretions, which sooner or later become infected. We then find an atelectatic, heavy and violet-coloured lobe with saccular bronchiectasis lying closely together.

The bronchial tree in such a lobe has few ramifications, but that does not mean that the disease is congenital. The description of the development of the bronchial tree by Bromann, Wilson and Miller explains that bronchiectasis following atelectasis in early childhood has a primitive, congenital appearance.

That lobar atelectasis often follows pneumonias in small children and that bronchiectasis often develops in those lobes has been clearly shown by Anspach (1939) in Chicago. By Roentgen examination of all pneumonias in small children he found lobar atelectasis in 1%, and more frequently in the lower lobes. It was more frequent in the two first years of life, and rare after the fifth year of life. He followed the children with Roentgen examinations at intervals. Some of the atelectases cleared up, and others persisted. In those which persisted one could follow the development of bronchiectasis. Through these investigations it has been clearly shown that pneumonias in small children followed by atelectasis is the most common cause of bronchiectasis in children and young people, and why these often have a primitive "congenital" appearance.

It can also be explained why children develop atelectasis after pneumonias more frequently than adults. It has already been mentioned that the bronchial tree is not fully developed until about the eleventh year. The infant's lung contains much more connective tissue, which is highly vascularized and contains an abundance of lymphatics. The alveoli are not connected by the fine communications, described in the adult by Koelliker. When therefore an infant gets pneumonia the connective tissue swells and closes the bronchi, and reaeration is much more difficult than in adults, specially in debilitated children with a weak cough.

Secondary bronchiectasis can have many origins.

Chronic bronchitis of sufficient duration and severity produces diffuse, cylindrical bronchiectasis due to the weakening of the bronchial wall, stagnation of secretions and perhaps the negative pressure during the first phase of coughing which exerts a considerable traction on the bronchial wall. These secondary bronchiectases are of no surgical interest.

Lung fibrosis as described by Corrigan (1838) is a frequent cause of bronchiectasis, e.g. following lung abscess which has proceeded into a chronic stage. The only radical cure of a chronic lung abscess is therefore a segmental resection, a lobectomy or even a pneumonectomy.

Tuberculosis often heals with so much

The bronchial tree had formed its final divisions and also the alveoli existed as small buds on the last ramifications of the bronchial tree. In monotremata and marsupialia such as the kangaroo the final divisions of the bronchial tree and the alveoli were only formed after birth and the newborn animals breathed through the primitive thin-walled bronchi. As long ago as in 1859 Hecker showed that the same thing could happen in premature babies. He described a baby born 2 months too early, who lived for 6 hours breathing and screaming. The autopsy showed that there were no alveoli and the baby thus had breathed through the bronchi as a kangaroo baby.

Bromann from Sweden showed in 1922 that the bronchial tree is not fully developed at birth. Then it has only few ramifications, but a dichotomic division of the bronchi continues up to the age of 11–13 years, and a constant formation of new bronchi and alveoli takes place. This has later on been confirmed by Wilson (1928), Miller (1934) and others.

Miller in 1934 gives the following description of the formation of congenital bronchiectasis based on the investigations of Bromann (1923), Wilson (1928) and himself. At birth the lung consists of abundant connective tissue into which the bronchi spread out from the hili-like fans—ending in the foetal bronchial buds. At the first respirations these buds open up and form the first alveoli, which are rather big and rather few in number. In the time which follows, new branches of the bronchial tree are formed in the periphery and from these new alveoli are constantly formed. The first alveoli which were formed right after the birth develop into the bronchioli of the adults and the peripheral bronchioli in the newborn develop into the major bronchi containing cartilage in the walls. By and by the bronchial tree spreads out and the connective, interstitial tissue attenuates.

TABLE 1. Schematical grouping of bronchiectasis according to origin.

I. *Congenital*		
Solitary		
Honeycomb		
Multiple		
II. *Infantile, atelectatic*		
Segmental	Lobar	Total	Increased negative pressure. Stagnant secretion. Infection. Cough.
III. *Secondary*		
Chronic bronchitis—diffuse cylindrical		
Lung fibrosis	Chronic abscess. Chronic empyema. Tuberculosis.	
Bronchostenosis	Stricture. Foreign body. Benign or malignant tumor. Extrabronchial.	

If no bronchial buds have been formed in the prenatal period, no alveoli will be formed at the first respirations, and the primitive bronchi will persist and dilate. This may take place in part of the lung or universal. The proximal part of the bronchi leading to the area may be pulled out to such an extent that they lose the connection with the area, and we now have a congenital cyst, which may be a solitary cyst or a multilocular cyst or multiple cysts according to the extent of the malformation and the stage in which the development of the lung stops. Congenital bronchiectasis and congenital cysts are thus only stages in the same congenital malformation by inhibition of growth.

Primary atelectasis in early childhood fol-

London during 3–6 years. 38 % died, but the treatment had been both medical and surgical. Of the 45 patients under medical treatment, 51 % had died, and of the 56 under surgical treatment 30 % had died.

Roles & Todd divided the patients into 3 groups: patients with a dry cough, patients with a productive cough, and patients with fetid sputum. In the first group 21 % died during observation time, in the second group 41 % died, and in the third group 86 % died.

Perry & King reexamined 400 patients from the Massachusetts General Hospital in Boston from 1926 to 1938. Of these 140 had been operated upon, 49 could not be traced. Of the remaining 211 patients 31 % had died.

Findlay & Graham (1931) followed 32 cases of bronchiectasis in children during 2–6 years. 37.5 % had died.

As will be seen, there is a good correspondence between the figures in all these statistics, showing that bronchiectasis as a rule is a progressive and very serious disease.

THE PROGNOSIS UNDER TREATMENT WITH ANTIBIOTICS

Very little can be said about this problem, because the treatment to-day is well established as a surgical treatment under cover of treatment with antibiotics. It would be very unreasonable to try to cure pronounced bronchiectasis with antibiotics alone, because it would seem impossible to sterilize the infection in the dilated bronchi where retention of the secretions would invariably make the inflammation flare up again, and resistance to antibiotics would finally develop.

TABLE 3. Results of surgical treatment in relation to the age of the patient at the time of operation. Rigshospitalet, Copenhagen.

(69 cases treated by dissection method and penicillin.)

	< 30 years		> 30 years		Total	
Well	14	81 %	6	42 %	20	59 %
Improved	11		10		21	
Unchanged or worse	4 = 13 %		11 = 28 %		15 = 22 %	
Hospital deaths	1 = 3 %		5 = 13 %		6 = 9 %	
Late deaths related to bronchiectasis	1 = 3 %		2 = 6 %		3 = 4 %	
Deaths due to other causes	0		4 = 11 %		4 = 6 %	
Total	31		38		69	

SURGICAL TREATMENT OF BRONCHIECTASIS

Primary mortality

As long as the operation still consisted in mass ligation of the lung pedicle with the tourniquet technique, lobectomy and pneumonectomy was frequently complicated by empyema and bronchial fistula. After the dissection and individual ligation of the structures in the pedicle became a routine procedure around 1944, these complications became much rarer and after the introduction of antibiotics they have indeed become very rare. Lindskog (1955) reports 42 % bronchial fistulas and 54 % empyemas prior to 1944, and only 2–3 % in 1951. Ochsner reports a reduction of empyemas from 55.5 % to 15.1 %, and of bronchial fistulas from 40 % to 6 %.

fibrosis and shrinking of the lung tissue that pronounced bronchiectasis follows. As the process is often localized in the apex of the lung, and the bronchiectases therefore are well drained, operation is often unnecessary. Chronic empyema with interstitial fibrosis may also produce bronchiectasis.

Bronchostenosis of all kinds produces bronchiectasis. It may be a stricture of a bronchus, either traumatic which is rare, or a healed tuberculosis of a bronchus, or an unspecific localized inflammation of the bronchus, as described by Legaard. A foreign body aspirated into the bronchial tree is a common cause in children, and in adults may be caused by dental extraction. Benign bronchial tumors and the potentially malignant adenoma produces bronchiectasis and it also accompanies malignant tumors, but the symptoms are here generally overshadowed by other symptoms caused by the tumor. Bronchostenosis caused by extrabronchial lesions is also well known. A common cause is shrinking of interbronchial lymphadenitis, mainly due to tuberculosis. This type of bronchiectasis is often localized and well treated by surgery.

THE PROGNOSIS OF BRONCHIECTASIS UNDER CONSERVATIVE TREATMENT

It is important to have exact information about the course of a disease without surgical treatment to evaluate correctly the results of the latter. Such statistics cannot be obtained to-day, but some have been gathered before surgical treatment began and are summarized in

TABLE 2. Mortality of bronchiectasis under conservative treatment.

Reference	Obs. time (yrs.)	No. of cases	Mortality (%)
Findlay & Graham (1931), (children)	2–6	32	37.5
Warner (1931)	8	110	23
Roles & Todd (1933)	3–6	106	38
Monod (1936)	3–11	141	31.2
Bradshaw (1941)	5–15	242	34.5

Table 2. One of the reasons why there are so few statistics is that bronchography was not introduced until 1922 by Forestier and Sicard, and before this investigation came into routine use neither an exact diagnosis nor the geographical extent of the disease could be determined.

Warner (1931) followed 110 cases up to 8 years; 23 % had died during the observation time.

Bradshaw, Putney & Clerf (1941) followed 242 patients from Jefferson Medical College Hospital in Philadelphia seen during the years 1925 to 1935, and reexamined in 1940. Of these 242 patients 34.5 % had died. Of the 59 patients who died, the cause of death in 6 cases was pneumonia, in 5 cases lung abscess or gangrena, in 5 cases brain abscess, in 5 cases myocarditis, in 3 cases hemoptysis, in 2 cases empyema, in 2 cases sepsis, in 2 cases suffocation in pus, in 5 cases spread of the disease in the lungs, and in 6 cases tuberculosis.

Monod & Bonniot followed 141 cases under conservative treatment with an observation time of 3–11 years and found that 31.2 % had died.

Roles & Todd (1933) followed 106 patients from the Brompton Hospital in

old. 102 patients (46 %) had residual bronchiectasis. Fifty-seven of these were contralateral, and the late result in this group showed 81 % good, 28 were ipsilateral, and the late result in this group showed 68 % good. Twenty-four patients had new formation of bronchiectasis, and the late result in this group showed 33 % good.

Lindskog and others from Yale University in 1955 published a report of a follow-up examination of 133 cases operated upon from 1937–1952. The results were good in 67 %, unchanged or worse in 27 %, and there were 6 % of deaths (4 primary and 4 late deaths). Of the surviving 129 cases, 32 had some remaining disease (=25 %). In the group without remaining bronchiectasis there were 44 % well, and 1 % deaths. In the group with some remaining disease there were only 9.4 % well and 9.4 % late deaths.

Our own series consists of 65 cases with an observation time from 2–6 years, operated upon from 1947 to 1953. The results were good in 63 %, unchanged or worse in 23 % and there were 14 % deaths (6 primary and 3 late deaths).

Of the surviving 60 patients one has not been reexamined. Of the remaining 59 patients 27 had residual bronchiectasis (=46 %). By analyzing the roentgenograms it looks as if 13 cases were new formed bronchiectasis. Of the 32 patients who had no residual bronchiectasis 18 were well, 9 improved, 5 unchanged or worse and there were no late deaths. Of the 27 patients with residual bronchiectasis only 2 were well, 8 improved, 10 unchanged or worse, and there were 3 late deaths caused by the disease.

The high percentage of remaining bronchiectasis in all series does not mean that they have been overlooked at the preoperative bronchography. In many cases it has simply not been possible to remove all diseased lung tissue, but the worst part has been removed in the hope of improving the patient's condition.

Comparing the results of conservative and surgical treatment of bronchiectasis, one must admit that the conservatively treated group is an unselected one containing all cases of bronchiectasis seen in the departments, and that the surgical groups are selected groups containing those cases which have been found fit for an operation. Milder cases have been discarded, because the disease has not been found serious enough to warrant the risk of an operation. Other cases have been found too advanced, either being in too bad a condition to tolerate an operation or too wide-spread to remove all diseased lung. In our own series the cases have largely been selected by medical colleagues. From the report from Lindskog and others it will be seen that only a few patients have been excluded because of too high an operative risk. Their future has been very gloomy. Some patients have been excluded, because they have been considered not to have sufficient extension of the disease or too mild symptoms. They have however done worse than the operated patients.

Generally speaking, about 70 % of the operated patients have had a good result of the operation, being either cured or very much improved. The primary mortality varies between 0.5 to

TABLE 4. Late results of surgical treatment

	Mayo Clinic 221 cases	Yale University 133 cases	Copenhagen 65 cases
Well	75 %	67 %	63 %
Unchanged or worse	21 %	27 %	23 %
Primary deaths 6	4 %	4	6 %
Late deaths 3		4	3	14 %

The primary mortality varies in statistics from recent years from 0.4 to 12 %. This variation is to a large extent due to the differences in the material. The age at the time of operation is an important factor, and so is the geographical distribution of the disease in the lungs.

Our own series

In Rigshospitalet, Copenhagen, from 1943–1953 we have operated upon 86 patients with bronchiectasis, on whom 100 resections have been performed, namely 16 pneumonectomies, 78 lobectomies, and 6 segmental resections. There were 8 bilateral lobectomies. (They were all cases of primary bronchiectasis; cysts, tuberculosis, and tumors have been excluded.)

The material has been divided into two groups, before and after the introduction of penicillin.

In the first years 7 patients were operated upon with the tourniquet technique. Five of them developed postoperative empyema. In the period 1943–1947 there were 31 resections with 11 postoperative empyemas, i.e. 35 %, and 4 of those died from the empyema. In the period 1948–1953 there were 7 postoperative empyemas in 70 operations, i.e. 10 %, and none of those died. In the last 3 years there has been only one death, caused by a lung embolism.

To-day we are only interested in the results of the operations which have been performed by the dissection technique of the lung pedicle, and under cover of treatment with antibiotics.

From 1947–1953 we have treated 69 cases with the dissection technique and penicillin given pre- and postoperatively. The primary mortality was 6 deaths out of 69 patients, i.e. 9 %. When we divide the patients into two groups, under 30 and over 30 years of age, we find that in the first group there is one death out of 31 cases, i.e. 3 %, and in the second group five deaths out of 38 patients, i.e. 13 %.

Comparing our material with a material from the Mayo Clinic, we find that in our material 55 % of the patients were more than 30 years old, and in the material from the Mayo Clinic only 12 %.

Late results

Follow-up examinations from recent years show that the most important factor determining the late results is remaining bronchiectasis or new development of bronchiectasis. To establish this very important fact one must have exact information about the pre- and postoperative bronchograms.

The Mayo Clinic has published a report in 1955 of 221 cases operated upon from 1942–1953. The results were good in 75 %, unchanged or worse in 21 %, and there were 4 % deaths (6 primary and 3 late deaths). Only 12 % of the patients were more than 30 years

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The Effect of Heparin upon Thermal Injuries to the Lungs

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A survey of the literature in recent years gives very little information about the problem of thermal injuries to the lungs and shows that no successful therapeutic measures, other than purely symptomatic ones, have been evolved. This is probably due to the fact that lung burns are not very common. However, when this type of injury does occur, especially in association with surface burns, the prognosis is often very bad. Therefore, a new effort towards a solution of the problem of treating these cases seemed indicated.

From previous reports on this subject, certain pathological findings deserved to be stressed. In dogs, Moritz, Henriques & McLean (1945) noted the escape of acidophilic serous fluid in the lumen of the affected alveoli and alveolar ducts, together with the presence of fibrin in the more serious injuries of this type. Fineberg, Miller & Allbritten (1954) found that the frothy pink fluid filling trachea and bronchi of burned dogs, had approximately the specific gravity of plasma. In human beings, the Report on the Management of the Cocoanut Grove Burns (1943) showed the presence of bronchi, completely occluded by plugs of fibrin, desquamated necrotic epithelium and leukocytes; also described were alveoles filled with serous exudate, vessels occluded by thrombi (in part at least antemortem), and atelectasis, involving sometimes a very important portion of the lungs.

Preliminary experiments with the burning technique described in this paper confirm these data. However, the presence of fibrin clots, sometimes of very important size, was frequently noted. These plugs unquestionably constitute an aggravating factor because they hinder elimination of fluid and débris accumulated behind them, or prevent inspired air from reaching often intact peripheral portions of lung parenchyma. It was therefore thought interesting to administer an anticoagulant.

This paper constitutes a report on the possible use of heparin in combating the effects of a steam-oxygen mixture upon air passages and lung tissue.

MATERIAL

Twenty-four adult mongrel dogs, numbered 1 to 24, weighing 12 to 27 kilograms, were used. These were subdivided into three groups of 8 dogs each.

10 %, but in the better group of patients below the age of 30 years is not higher than 3 %.

Surgical treatment should be the choice, whenever it is possible, and the operation should not be delayed, if the symptoms and the extent of the disease is not negligible. One should be very active in the younger age group. The operation should be as radical as possible; the place for segmental resection is a very limited one.

PREVENTION

Most of the so-called primary or lobar bronchiectases are caused by lung infections in the early childhood, and most of them occur in small and debilitated children suffering from malnutrition and vitamin deficiency. These children develop atelectasis and bronchiectasis more often than healthy children. Preventive treatment of bronchiectasis therefore means higher living standard, better nutrition and good medical care of children with lung infections, including treatment with antibiotics.

In Denmark this type of bronchiectasis is becoming more and more rare, and the cases which we still see are diagnosed earlier, and sent to the thoracic surgeons at an earlier stage of the disease. The cases which we used to see twenty years ago bringing up ounces of foetid sputum, and which are included in the series, and form the basis of the present analysis, have now almost disappeared.

This also confirms that bronchiectasis is mainly an acquired disease. If 80 % were congenital the disease would not have become as rare as it is to-day.

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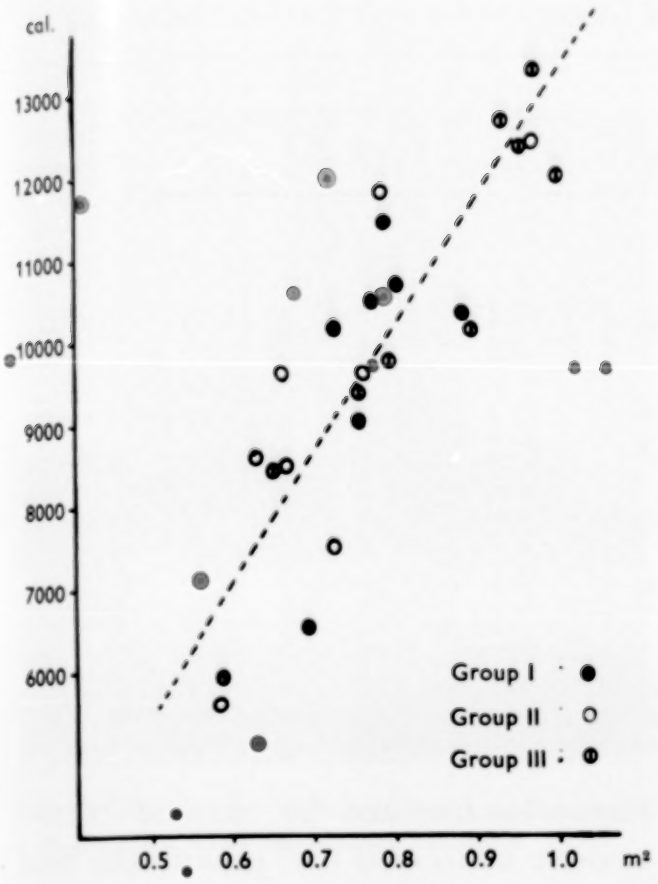


FIG. 2. Relation between body surface and amount of calories administered. The dotted line indicates the desired relationship.

when the dog had received approximately the predetermined amount of calories. The exact amount of calories given was then calculated from calibration data, calorimetric measurements and the burning time. The latter lasted from 4 to 8 minutes. The relation between given and predetermined amount of calories is given in Fig. 2.

Follow-up-procedures.—Immediately after burning, the dogs were put in a moderate Trendelenburg position in order to facilitate collection of secretions from the tracheal tube. Electrophoresis was carried out on some samples of this fluid. The cuff of the McGill tube was deflated, but the tube itself left in place until the animal awakened and coughed it up. Large doses of penicillin (900,000 IU/day) and stretomycin (1 gram/day) were given, and this treatment continued up to 10 days. The dogs were allowed to die spontaneously or sacrificed after a period of 21 days to one month. Autopsies were carried out on most of the animals, and the macroscopic pathological findings noted.

RESULTS

Blood serum and tracheal secretions

In all dogs, rales could be heard over both pulmonary fields, less than ten minutes after the burn was carried out. In group I, frothy pink fluid, of high viscosity containing fibrinous strands started to flow from the tracheal tube after 30 to 45 minutes. In most of the samples a gelatinous clot formed shortly after collection.

In group II, this fluid started to flow usually after 15 to 20 minutes, and was less viscous in character. No fibrinous strands were observed. Gelatinous clots formed in the tubes only after addition of protamine sulfate to the samples. Average values for total protein content were found to be 5.9 g % in blood serum, and 5.2 g % in the secretions. Results of electrophoresis carried out on blood serum, and tracheal fluid taken one hour after burn from two dogs in group I, and two dogs in group II, are given in Table 1.

Survival time

In group I, all dogs died spontaneously within 20 to 69 hours. In group II, five dogs died spontaneously within 5 to 34 days. Three dogs were sacrificed after 21 and 30 days. In group III, five dogs died

In group I, the dogs were burned without any treatment and constitute the control series. In group II, 4 milligrams of heparin per kilogram body weight were administered intravenously 10 to 15 minutes before burning. In group III, the same dose of heparin was given one hour after the burn was sustained. In groups II and III, a second dose of heparin was administered four hours after the first.

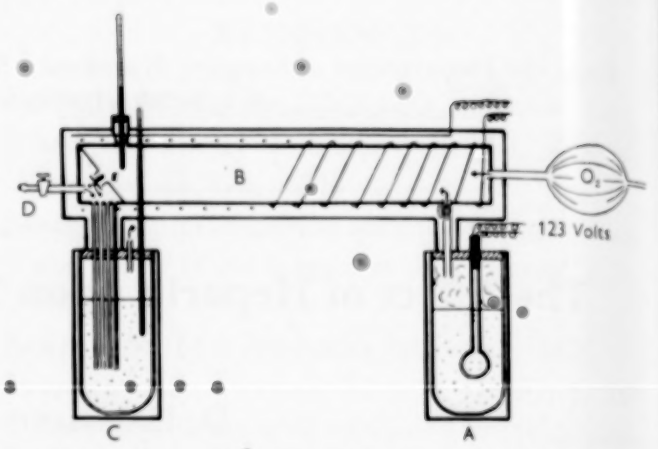


FIG. 1. Diagram of apparatus used in producing pulmonary burns. (A) Steam generator; (B) mixing and temperature-stabilizing chamber; (C) calorimeter; (D) outlet tap and connecting piece to endotracheal tube; (E) valve directing expired gases and excess steam mixture to the calorimeter.

METHODS

ANESTHESIA.—Nembutal or sodium pentotal, up to 20 mg/kg body weight, was injected intravenously. The smallest possible amount of anesthetic was used in order to induce a sufficiently deep anesthesia, but of short duration. Tracheal intubation was then carried out using a McGill tube (no. 9 or 10) with inflatable cuff. During these experiments, the animals were always allowed to breath spontaneously.

Body surface.—This value was calculated according to the formula given by Cowgill and Drabkin (1927):

$$S = K \times \mathrm{Wt}^{\frac{2}{3}};$$

S in square meters; Wt in kilograms; $K = 0.112$.

Analysis of blood serum and tracheal secretions.—The total protein concentration was determined ad modum Kjeldahl. Paper electrophoresis of the proteins in blood serum and the collected secretions was carried out in veronal acetate buffer (pH 8.4, ionic strength 0.1) for 16 hours with 1.5 mA per strip.

Administration of moist heat.—The dogs were allowed to breath a steam–oxygen mixture containing 75–80 % steam. In order to be able to compare results in the three groups, it was necessary that all the animals received an equivalent amount of heat. In these experiments, each dog was given a number of calories proportional to the body surface. The number of calories administered per unit of body area was chosen arbitrarily, but only after preliminary experiments had shown that this amount of heat always caused untreated dogs to die within 3 days. The breathing mixture was generated by an apparatus consisting essentially of a steam generator, a mixing and temperature stabilizing chamber, and a calorimeter (see Fig. 1). The apparatus was calibrated, i.e. its total caloric output determined, before each burn. The amount of heat absorbed by the dog's respiratory tract, at any given moment, was equal to the difference between the total caloric output from the apparatus and the amount of calories taken up by the calorimeter. The progression of heat uptake could thus be followed and the burn halted

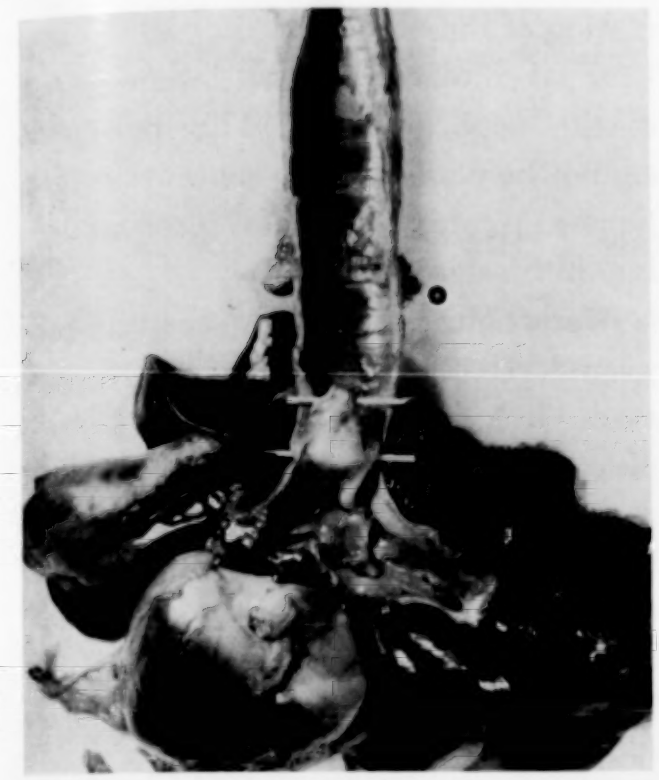


FIG. 4. Dog no. 7. Aspect of lungs and airways at autopsy, three days after burning.

bifurcation occluding both main bronchi (see Fig. 4).

In group II, six animals out of eight were examined. None of them had fibrinous membranes or plugs. Dogs nos. 9 and 13 had normal lungs. Dogs nos 14 and 15 had scattered atelectasis and moderate edema. Dogs nos. 10 and 12 had signs of infection of bronchopneumonic type associated with a severe tracheal stenosis.

In group III, four dogs (nos. 17, 22, 23 and 24) had normal pulmonary findings. Two dogs (nos. 20 and 21) had scattered atelectasis and moderate edema. Two dogs (nos. 18 and 19) had large fibrinous membranes in their main bronchi, as well as atelectasis and edema.

(B) *Trachea.*—In all three groups, the tracheal lesions were severe and had a sharply defined upper limit corresponding to the cuff of the McGill tube.

In group I, all animals showed intense

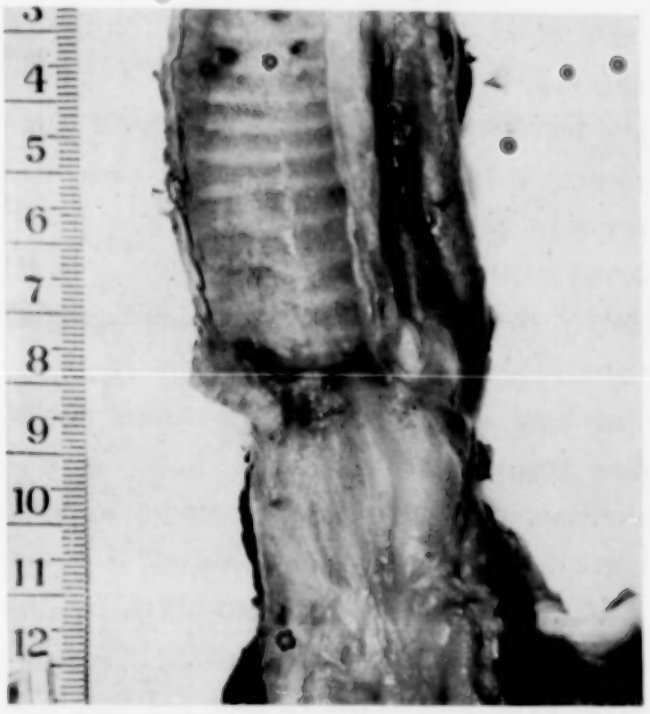


FIG. 5. Dog no. 10. Typical aspect of severe tracheal stenosis 21 days after burning.

congestion and ulceration of the tracheal mucosa. Peritracheal and mediastinal edema were also present.

In groups II and III, 12 dogs out of 14 examined developed a stenotic process located at the junction of the normal and pathological portions of the trachea. Dogs nos. 9, 13, 22, 23 and 24 had a moderate stenosis. Dogs nos. 10, 12, 14, 15, and 17 had a very severe stenosis of 4 to 5 millimeters in diameter (see Fig. 5). A total collapse of the trachea was observed in dogs nos. 20 and 21. Of the dogs not autopsied, one (no. 16) showed extreme respiratory distress, and pronounced wheezing, indicating the probable presence of a tracheal stricture.

DISCUSSION

In group I, the control series, all the animals died after a longer interval than that reported by Aviado and Schmidt (1952) on the one hand, and by Fine-

TABLE 1. Electrophoretic comparison of blood serum and tracheal secretion.

	Tot. protein g%	Albumin	Globulin % of total	α_1	α_2	β	γ	Albumin/ Globulin
Group I								
Dog no. 7								
Serum	6.1	49.8	50.2	5.7	11.4	21.8	11.3	0.99
Secretion	4.7	57.0	43.0	4.7	8.8	21.2	8.3	1.32
Dog no. 8								
Serum	4.3	47.3	52.7	8.4	9.8	20.3	14.2	0.90
Secretion	4.7	54.6	45.4	8.3	11.6	10.5	15.0	1.20
Group II								
Dog no. 11								
Serum	6.7	47.0	53.0	8.6	6.7	26.0	11.7	0.89
Secretion	5.5	50.5	49.5	6.7	9.0	22.5	11.3	1.02
Dog no. 12								
Serum	6.6	52.1	47.9	9.2	6.1	27.2	10.4	1.09
Secretion	6.0	57.6	42.4	5.8	7.6	15.7	13.3	1.36

spontaneously within 3 to 26 days. Three dogs were sacrificed after 21 days. The individual survival times are given in Fig. 3.

Postmortem findings

(A) *Lungs.*—In group I, all the animals showed a very uniform pulmonary picture, characterised by marked edema, massive atelectasis and pink frothy fluid partially filling the bronchial tree. In all cases, fibrinous membranes were observed in various bronchial sections, ranging from the main bronchus to the segmental bronchi. In one dog (no. 7), a large such membrane filled the whole

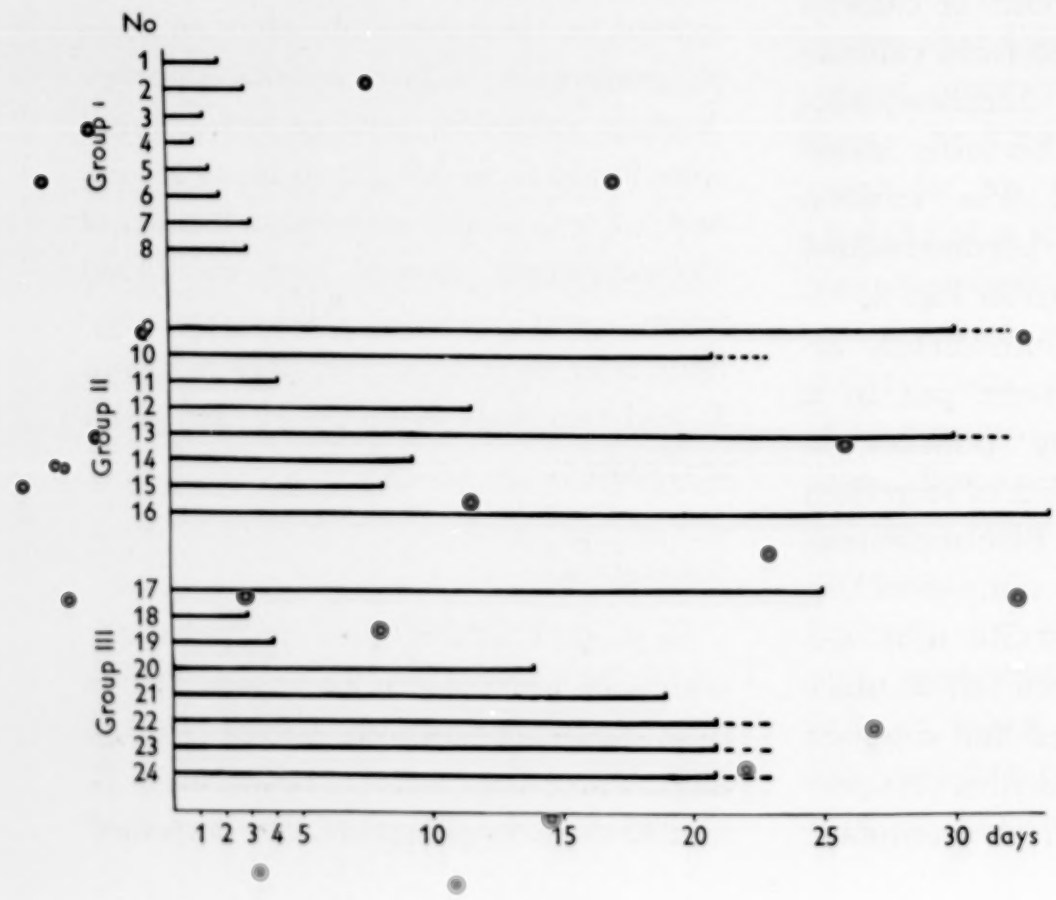


FIG. 3. Individual survival times. Dotted lines indicate sacrificed animals.

ACTA CHIRURGICA SCANDINAVICA, SUPPL. 245: 91–112, 1959

From the Clinic for Thoracic Surgery, Karolinska Sjukhuset, Stockholm, Sweden

Twenty-one Years of Thoracic Injuries

A clinical study of 313 Cases

L. Johansson and T. Silander

During the years 1938–1958 the population of Stockholm has increased by 394,169 persons. During the same period the number of motor vehicles has increased by 93,903. Traffic accidents have come to be one of our biggest injury-groups as regards both degree of seriousness and number. Kenney & Schlosser (1958) state that 25 % of fatal traffic accidents in America refer to thoracic injuries, and they estimate that only one of four persons with thoracic injuries from such accidents survive with conventional treatment.

We have tried to find out whether the number of traumatic thoracic injuries has increased in recent years, to ascertain the percentage of such injuries due to traffic accidents and to what extent changed views as to treatment may have affected the final result.

With this aim in view we have analysed the thoracic injuries which during the years 1938–1958 have been treated at the Sabbatsberg Hospital and during the years 1957–1958 at the Clinic for Thoracic Surgery at Karolinska Sjukhuset. Thoracic injuries due to the inhalation or swallowing of foreign bodies or injurious substances have not been included.

We have divided up the material into two main groups, viz., non-penetrating or crushing injuries and penetrating injuries. By crushing injuries we understand all traumatic injuries in which there is no wound through the thoracic wall. Within this group we have made a further division, treating injuries with fractures of the thorax skeleton in a special sub-group and traumatic bronchial rupture, traumatic aortal aneurysm and traumatic myocardiac injuries respectively in sub-groups of their own. In the group referred to as penetrating injuries we have made a corresponding division into sub-groups, viz., cases with lung injuries and cases with injuries to the heart or large vessels.

1. CRUSHING INJURIES TO THE CHEST

A. Injuries with Fracture of the Thoracic Skeleton

Analysis of the material

This group comprises 293 cases, including 219 men and 74 women. The age

berg *et al.* on the other. The cause of this may be due to the difference in burning techniques. These authors used pure steam, without any knowledge as to the amount of calories given. Aviado *et al.*, using a burning time of 12 to 120 seconds, had 8 immediate deaths and a survival time of 15 to 120 minutes on 18 dogs. Fineberg *et al.*, using a burning time of one minute on 14 dogs, had no immediate deaths and an average survival time of 5 hours and 47 minutes.

With a standardized amount of calories absorbed by the animals, the survival time in groups II and III was appreciably longer than that in group I. Although most of the dogs in those two groups did die spontaneously, death was essentially due to the development of a tracheal stricture. Since this stenosis was always located at the same level, coinciding with the extremity of the tracheal tube, it constituted essentially a late consequence of intratracheal administration of moist heat. The pathological findings in the lungs of these dogs were much less pronounced than in group I and in several cases could directly be ascribed to the tracheal stenosis.

The only apparent reason for prolongation of the survival time in groups II and III lies in the anticoagulant effect of heparin. This affirmation is supported by the results of the analysis and observations of the collected secretions, and by the total absence of macroscopical fibrin plugs in group II.

In group III, dogs nos. 18 and 19 developed large fibrin plugs. In all probability, pulmonary exudate had collected in bronchi and had coagulated before heparin was injected. The formation of these plugs could perhaps also have taken place after the disappearance of the heparin effect. This possibility cannot be denied, but a more prolonged heparin treatment ought to prevent such late fibrin deposits.

Many questions still remain unanswered. Heparin can keep the air passages free from obstructive fibrinous plugs, and probably thereby prolong the survival time in cases of thermal injuries of the respiratory tract. However, heparin must be administered at the earliest possible moment after the burn. Further investigation in this direction is necessary.

SUMMARY

A method for producing experimental lung burns, with administration of a standard amount of calories, is described. Survival times of burned dogs treated with heparin were prolonged, in comparison to those of untreated dogs. Causes of death and pathological findings are analysed.

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TABLE 4. Distribution and combinations of injuries.

No. of cases	Rib fractures	Sternum fractures	Fracture of extremities	Skull fractures	Commotio	Pelvis fractures	Fractures of vertebrae	Luxation	Distortion	Contusion	Misc.
165	+	...	...	...	...	...	...	...	...	...	...
7	...	+	...	...	...	...	...	...	...	...	...
5	+	+	...	...	...	...	...	...	...	...	...
24	+	...	+	...	...	...	...	...	...	...	...
2	+	...	+	...	+	...	...	...	...	...	...
1	+	+	+	...	...	...	...	...	...	...	...
1	+	+	...	...	+	...	...	...	...	...	...
1	+	+	...	...	...	...	...	+	...	...	...
1	+	+	...	...	...	...	+	...	...	...	...
1	+	+	...	+	+	...	...	...	...	+	...
1	+	+	+	...	...	+	+	...	...	...	...
2	+	...	...	+	+	...	...	...	...	...	...
1	+	...	...	+	+	...	...	...	...	+	...
1	+	...	...	+	+	...	...	+	...	...	...
2	+	...	+	+	...	+	...	...	...	...	...
1	+	...	+	...	...	...	...	...	...	+	...
17	+	...	...	...	+	...	...	...	...	...	...
6	+	...	...	...	+	...	...	...	...	+	...
1	+	...	...	...	+	...	...	+	...	...	...
3	+	...	...	...	...	...	...	+	...	...	...
1	+	...	...	...	...	...	...	...	+	...	...
21	+	...	...	...	...	...	...	...	...	+	...
2	+	...	+	...	...	...	...	...	...	+	...
4	+	...	+	...	...	+	...	...	...	...	...
1	+	...	+	...	...	...	...	...	...	...	+
1	+	...	+	...	...	+	+	...	...	...	...
1	+	...	+	...	...	+	...	...	...	+	...
1	+	...	+	...	...	...	+	...	...	+	...
2	+	...	+	...	...	...	...	...	...	+	...
2	+	...	+	...	+	+	...	...	...	...	...
1	+	...	+	+	+	+	...	...	...	...	+
4	+	...	...	...	...	+	...	...	...	...	...
1	+	...	...	...	...	+	...	...	...	+	...
3	+	...	...	...	...	...	+	...	...	...	...
1	+	...	...	...	+	...	+	...	...	...	...
1	+	...	...	...	...	...	+	...	...	...	+
1	+	...	...	...	...	+	...	...	...	+	+
1	+	...	...	...	...	...	...	...	...	+	+

Extent and localization of the injuries

In 172 cases the fractures involved only the ribs or sternum. In the remaining 121 cases these were combined with other injuries. Their number is shown in Table 3 and the various combinations in Table 4.

The total number of ribs fractured in one or several places was 932. The distribution of the fractures among different ribs is shown in Fig. 2. Of all the fractures 51.3 % were localized to ribs VI–IX. In 18 cases the fractures were bilateral, in 117 right-sided and in 143 left-sided. In 7 cases there are no data as to side and in 11 cases no data as to the number of

TABLE 1. Distribution according to age.

Age groups	No. of cases	Age groups	No. of cases
10–19	7	70–79	32
20–29	25	80–89	6
30–39	35	90–99	1
40–49	49	Av. age	51.8
50–59	80	No. of females	74
60–69	58	No. of males	219

varies between 13 and 91 years and is on an average 51.8 years. The age distribution may be seen in Table 1. The period of hospitalization is on an average 14.8 days. During the period 1938–1948 the average period of hospitalization was 12.8 days and during the period 1949–1958, 15.5 days.

Mode of infliction of the injuries

107 persons had been injured in traffic accidents, to which cause were thus due 36.5 % of all injuries.

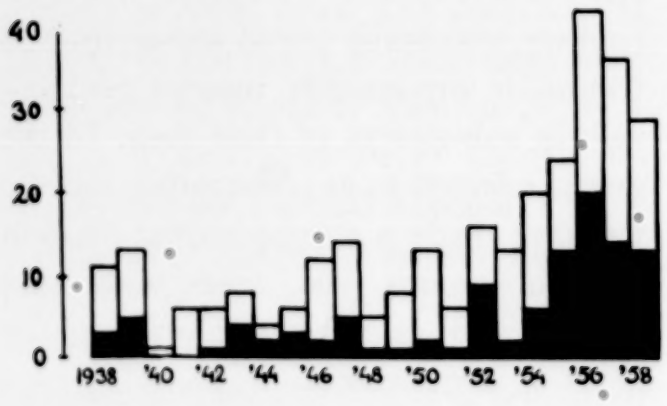


FIG. 1. Annual distribution of 293 cases with fracture of thoracic skeleton. Blocked-in columns designate traffic accidents.

The distribution of the injuries over the years and the percentage constituted by traffic accidents emerge from Fig. 1.

The mode of infliction is seen in Table 2.

TABLE 2. Mode of infliction of the injuries.

Mode of infliction	Number of cases
Traffic accidents	107
Falls from a height	81[a]
Fall down steps	18
Fall on same plane	67
Struck by falling object	8
Manhandling, fighting or sport	5
Crushing injuries	6
Trampled or kicked by animal	2

[a] Including 7 jumps with suicidal intent.

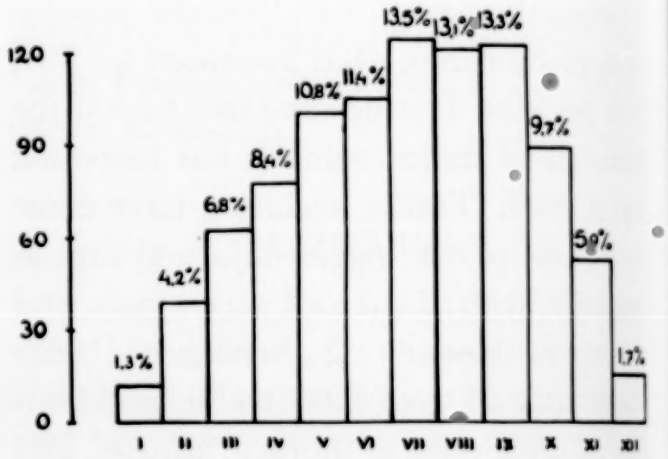


FIG. 2. Distribution among different ribs of 932 rib fractures.

TABLE 3. Simultaneous occurrence of injuries other than rib fractures.

The table shows only the number of the injuries; their various combinations are shown in Table 4.

Injury	Number
One or more fractures of sternum	18
One or more skull fractures	11
One or more pelvic fractures	15
One or more fractures of one or several extremities	46
One or more fractures of one or several vertebrae	6
Co mmotio	40
Contusion	39
Luxation	6
Distortion	1
Hepatic rupture	1
Injuries to kidneys or urinary passages (hematuria)	43

injured persons during the years 1945–1958 was 244. Of these, 56.6 % were given such treatment.

Mortality

In 15 cases the injuries had a fatal issue, implying a mortality of 5.1 %.

By way of illustrating the difficulty of deciding the importance of the thoracic injuries for the fatal issue, we give here a summary epicrisis of the 15 cases.

Account of the 15 fatal cases

1. 1567/41. 39-year-old man, admitted with seriously affected general condition after fall from scaffolding. Despite blood transfusion, irreversible state of shock causing death within a couple of hours. Autopsy.

Diagnosis: Fracturae multiplex costarum et pelvis + shock + fat embolisms?

2. 1897/44. 88-year-old man. Knocked down by bus while crossing street. At first recovered from shock but died on second day from pneumonias. Autopsy.

Diagnosis: Fract. costae II–IX dx. et III–X sin. + bronchopneumoniae pulm. amb.

3. 3000/52. 64-year-old man. Knocked off bicycle by bus. Admitted unconscious with fully developed state of shock that proved irreversible despite intensive treatment. Died 4 hours after admission. Autopsy.

Diagnosis: Fract. costae multipl. amb. + Fract. pelvis c. ruptura urethrae.

4. 10425/52. 57-year-old man. Admitted unconscious after 4-meter fall from scaffolding. Subcutaneous emphysema, pneumothorax and hemothorax. More deeply unconscious. Bronchoscopic suction second day. On fourth day tracheotomy to enable bronchial toilet. Died on morning of fifth day. Autopsy.

Diagnosis: Fract. costae II–IX sin. + Fract. claviculae sin. + Commotio cerebri + Fract. cranii + Haematoma subdurale.

5. 9541/53. 33-year-old man. Seriously affected general condition after 6-meter fall from cable conveyer. First day improvement but second day coughing up of fresh blood and sudden worsening. Taken to operating department for tracheotomy which was not, however, performed, as bronchoscopic suction resulted in clean bronchial tree. Half an hour later further worsening and death. Autopsy.

Diagnosis: Fract. costae III–V sin. et os ilei bilat. + Haemothorax + Contusio lob. inf. pulm. sin. et contenta sanguina viae respiratori et ventriculi + Ruptura hepatis et ren. sin. + Haematoma retroperitoneale.

6. 6439/54. 71-year-old woman. Jumped from third floor with intent to commit suicide. Shock just after admission. Abdominal status indicated hemorrhage or rupture of organ and exploratory laparotomy was accordingly performed; negative findings. Reduction of forearm fractures. Four hours after operation died of shock. Autopsy.

Diagnosis: Fract. cost. III–V dx. + Fract. os ilei dx. + Fract. antebrachii dx. + Fract. fibulae sin. + Infarctus cordis + Haematoma retroperitoneale.

7. 7575/54. 49-year-old woman. Jumped from second floor with intent to commit suicide. Seriously affected general condition. Numerous fractures. Shock. Increasing stupor. Died second day. Autopsy.

Diagnosis: Fract. multiplices costarum, pelvis, antebrachii amb., sterni et vertebrarum lumbal. + Haemothorax + Haemorrhagia subdural. minimal. + Oedema pulm. et cerebri.

8. 2341/55. 34-year-old man. Crushed between bus and wall. General condition affected. Cyanosis. Taken to operating department after X-ray. Intubated and given positive-pressure respiration during preparations for tracheotomy. Cardiac arrest and death before there was time for operation. Died three hours after admission. X-ray showed, apart from fractures, pneumothorax, hemothorax and subcutaneous emphysema. Medicolegal autopsy of which findings not given.

Diagnosis: Fract. costae multipl. bilat. c. pneumothorax et haemothorax dx. + Emphysema subcut. + Atelectas. pulm. bil.

9. 12934/55. 59-year-old man. Fell from fifth storey while clearing snow from roof. Admitted with deep shock and affected general condition. Not possible to palpate radial pulse 2 hours after admission. Tracheotomy performed and patient put in respirator. In the meantime carotid pulse had also stopped: thoracotomy and heart massage

injured ribs. In 7 cases there was only fracture of the sternum without other injury. The number of fractured ribs per patient varied between 1 and 14, the average being 3.3.

In 11 patients it was the first rib that was fractured. In one case the fractures were bilateral, in 6 right-sided and in 4 left-sided. Four of the 11 patients had simultaneous fractures of the clavicle.

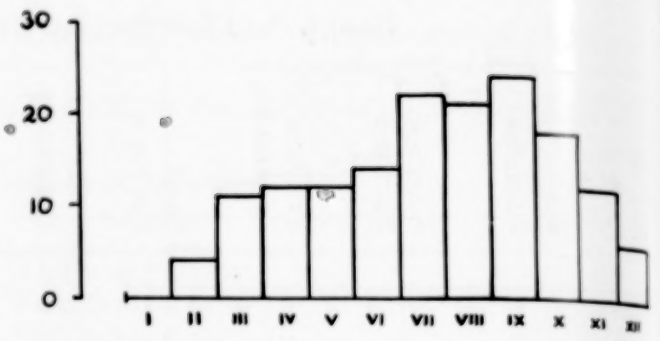


FIG. 3. Distribution among different ribs of 156 rib fractures in 40 cases with hematuria. Possible other injuries have not been considered.

Complications from pleura, lungs and urinary passages

Pneumothorax, hemothorax and subcutaneous emphysema occurred in 163 cases, or 55.6 %. Hemothorax occurred in 158 cases, pneumothorax in 78 and subcutaneous emphysema in 48 cases. The distribution of these complications and their combinations emerge from Table 5.

Temporary parenchymal induration indicating hemorrhage in the lung is reported in 53 cases.

Hematuria occurred in 43 cases. There are no data as to sediment in 70 cases. Thus at least 14.7 % of the cases had signs of injury to the kidney or urinary passages. In 40 of the hematuria cases there were, apart from other injuries, 156 rib fractures, including 54.5 % involving ribs VII–X. The distribution of the fractures over different ribs is shown in Fig. 3. In one hematuria case there was only fracture of the sternum and in one there is no information as to the localization of the fracture.

TABLE 5. Distribution of hemothorax, pneumothorax and subcutaneous emphysema in 163 cases.

	No. of cases
Pneumothorax + hemothorax + subcutaneous emphysema	30
Pneumothorax + hemothorax	45
Pneumothorax + subcutaneous emphysema	2
Pneumothorax only	1
Hemothorax + subcutaneous emphysema	14
Hemothorax only	69
Emphysema only	2

Treatment

Pleural puncture was performed 118 times on 52 patients. Permanent intercostal suction drainage (Bülau drainage) was applied in 26 cases. Intercostal blockade was applied in at least 22 cases. Four cases required acute operation, 4 were bronchoscoped and in one case positive-pressure respiration was given after intubation.

Tracheotomy was performed in 19 cases and respirator treatment given in 12 cases. Of the 19 tracheotomies, one was performed in 1952, four in 1955, seven in 1956, three in 1957 and four in 1958. Six of the fatal cases were tracheotomized. They are described in detail below.

Treatment with antibiotics and/or chemotherapeutic agents was given in 138 cases during the years 1945–1958. As emerges from Fig. 1, the number of

arkable that during the first 11-year period the hospitalization was of shorter duration (12.8 days) than during the last 10-year period (15.5 days). We have taken this as an expression of an increased degree of seriousness in the injuries, especially as the growing shortage of beds in recent years has led to greater stringency as regards the indications for admission and to a general cutting down of the period of hospitalization. The same trend is also illustrated by the fact that, of the 15 fatal cases, 13 fall within the last period.

Traffic accidents caused 36.5 % of the injuries. Of the 107 traffic accidents, only 24.6 %, as appears from Fig. 1, occurred during the first 11 years, while 75.4 % occurred during the period 1949–1958. No less than 62.3 % of the traffic injuries happened during the five-year period 1954–1958. However, also the total number of injuries shows approximately the same increase, 70.6 % falling within the last 10-year period and 51.5 % during the last five-year period. Even if there is an increase in the absolute number of traffic accidents, the percentage of thoracic injuries among them has not increased to any appreciable extent in this material. A possible explanation is that the patients derive exclusively from a city, where narrow streets, density of traffic and speed limit have prevented traffic accidents due to high speed. In consideration of these circumstances, no more detailed analysis of the traffic accidents has been thought to be indicated. A certain part of the increase of injuries in the course of the years may be explained by the growing number of remittances from other hospitals, running parallel with the increase in thoracic surgical activity at the Sabbatsberg Hospital.

It is very difficult to assess the role of rib fractures in the large number of cases (41 %) in which they have been combined with other injuries. The number of other injuries and their degree of seriousness may be seen in Tables 3 and 4. Eleven of the fatal cases had combined injuries. Cameron *et al.* had 60 % of combined injuries in their material.

The distribution of rib fractures over the different ribs is in agreement with that found in the literature. We have not found any predominance for either the right or the left side. Nor have we been able to find any consistent traumatic explanation of the fractures of the first rib based upon the varying modes of infliction of the injuries.

More than half of the cases had some complication from the pleura or lungs. We have included all cases with fluid in the pleura verified by X-ray, even if the exudation has been only slight. Thus the majority of hemothorax cases have not required active treatment. In 64 cases the pleura has been punctured or drained. No fewer than 118 pleural punctures have been carried out on 52 of these patients. Permanent drainage has been established in the case of patients with major pneumothorax or in whom pleural puncture has not given lasting results. This was done in 26 cases. Both pneumothorax and hemothorax imply a considerable risk of functional impairment of the lung, acutely and on a longer view. In order to increase the vital capacity and prevent thickening of the pleura, the air or fluid in the pleura must always be removed as completely as

without effect. Died 3 hours after admission. Medico-legal autopsy.

Diagnosis: Fracturae costarum I–X sin. cum laesio. lob. inf. pulm. sin. et pleurae + Contusio pulm. dx. + Fract. humeri sin. + Fract. pelvis cum laesio urethrae.

10. 1402/56. 64-year-old woman. Jumped from third floor with intent to commit suicide. Moribund on admission. Was given 9 bottles of blood in rapid succession but state of shock persisted. Cardiac arrest and death four hours after admission. No autopsy.

Diagnosis: Fract. costae XI–XII dx. + Fract. comminut. pelvis + Fract. colli fem. lat. dx.

11. 12386/56. 77-year-old man. Knocked down by tram-car while on foot. Admitted unconscious with extensive subcutaneous emphysema. Tracheotomy and respirator treatment. Following day more deeply unconscious with hemiplegia, pos. Babinski and rising non-protein nitrogen. Died on evening of same day. Medico-legal autopsy.

Diagnosis: Fract. costae multipl. + Fract. cranii + Contusio cerebri.

12. 12286/56. 68-year-old woman. Knocked down by motor-car. Admitted in developed state of shock. Numerous fractures. Anti-shock treatment + extension of fractures. After temporary improvement died 3 days after the accident. Medico-legal autopsy.

Diagnosis: Fract. costae X dx., pelvis, diaphys. fem. amb., malleol. med. ped. dx. et claviculae dx. + Vuln. contus. reg. occipit. et crur. dx.

13. 12401/56. 79-year-old man. Trampled by cow. Remitted from another hospital on account of paradoxical respiration. Immediate tracheotomy and respirator resulting in distinct improvement. On the seventh day sudden major gastric hemorrhage and death before anything could be done. Autopsy.

Diagnosis: Fract. manubrii sterni, costae II–IX sin. et cost. II dx. + Haemothorax + Ulcus ventriculi c. haemorrhagia ac.

14. 10512/56. 28-year-old man. Crushed under tractor. Admitted in affected state to another hospital, where on suspicion of abdominal injury laparotomy was performed. A good deal of blood was found in the abdomen, but no other source of bleeding than a retroperitoneally located hematoma. The day after the operation remitted to Sabbatsberg Hospital. Died on the third day after the accident. Medico-legal autopsy.

Diagnosis: Fract. costae IV–VI sin. + Contusio abdominis et thoracis. + Fract. os pubis bilat. et os ischii sin. + fat embolisms.

15. 4761/57. 71-year-old man. Found lying on the floor at home. Admitted with respiratory difficulties and cyanosis. At first interpreted as cardiac infarct and admitted to medical department. X-ray revealed fractured ribs and ECG gave not evidence of infarct. Was therefore transferred to surgical department the day after admission. Respiratory insufficiency. Tracheotomy and respirator on third day. Died a couple of hours after the tracheotomy. Autopsy.

Diagnosis: Fract. costarum III–V sin. + Cardioarterioscleros. + Oedema pulm.

Discussion

The age distribution (Table 1) shows a maximum in the age groups between 40 and 70 years. This agrees with the results from a material described by Knoepp (1941) and Cameron, O'Rourke & Burt (1949), as also with the well-known circumstance that skeletal brittleness increases with age.

We have included in our material all cases of rib fracture independently of the degree of other concomitant injuries. In a few cases, especially during the first years in the series, there has been no X-ray examination, yet there has been no doubt as to the diagnosis at the physical examination. An X-ray examination would certainly, even in these cases, not have altered the therapeutic result, but might possibly have affected our statistics relating to pneumothorax and hemothorax. We consider, in principle, that an X-ray examination is necessary for the adequate treatment of rib fractures.

The period of hospitalization was on an average 14.8 days. We think it rem-

of carbon-dioxide retention leads automatically to quick therapeutic activity. Much more difficult is the judging of the apparently only moderately affected patients who are a little strained while in the X-ray department and have had time to get an oxygen tube inserted in the nose and have not been considered to need continuous observation. A carbon-dioxide retention may be effectively masked right up to the point of a rapid worsening that may prove fatal. Only with blood-gas analyses, which may be carried out in arterial or venous blood, is it possible to make quite sure whether there is carbon-dioxide retention or not. Astrup has described a quick method for these analyses. From the clinical viewpoint it is, of course, better to foresee a complication than to treat one that has already occurred. In this connection attention may be drawn to Carter's investigations on tracheotomy from 1951, where he showed the favourable influence of tracheotomy in severe thoracic injuries. Carter ascribed the favourable effect to the reducing of the resistance in the respiratory passages and of the dead space and to the frequent suctions applied to the respiratory passages. Jensen (1952) showed clinically that coughing is ineffective in patients with thoracic injuries, which speaks in favour of tracheotomy, since external devices for the stabilization of the thoracic wall cannot effectively eliminate the paradoxical respiration and are, moreover, difficult to apply. Jensen also gave an account of the necessary measures for the improvement of the respiratory capacity reduced by thoracic injury. In many cases satisfactory ventilation cannot be maintained despite such suitable aids (Jensen). It is then necessary to have recourse to artificial respiration. Several apparatuses for this purpose have been constructed in recent years.

Mörch has described a type of respirator that he has been using since 1940. Through hyperventilation through an uncuffed cannula this respirator gives an alkalotic apnea with extinction of the activity of the respiratory musculature. Good results with this respirator have been reported by several writers (Avery, Trier-Mörch & Benson, 1956; Avery, Head, Hudson & Bennett, 1957; Kenney & Schlosser, 1958).

We have used a volume-cycled respirator according to Engström and the ventilation has been calculated in advance with the help of a handy nomogram.

Principles of treatment in cases of severe thoracic injuries

In dealing with thoracic injuries the treatment of shock, the sucking out of hemopneumothorax and the establishing of a free respiratory passage are all equally important and urgent measures. The free respiratory passage must be ensured with intubation either through bronchoscope or endotracheal tube. The respiratory passages are sucked clean and positive-pressure respiration is administered. A tracheotomy may then be performed with the tube in place. As the only satisfactory method of examination of thoracic injuries is that by X-ray, this should be carried out as soon as possible. It must not be forgotten that an X-ray examination with the patient in the recumbent position cannot cer-

TABLE 6. Mortality for cases of acute fractures of thoracic skeleton.

Reference	%
Findlay, 1937	24.5
Hinton & Steiner, 1940	10.4
Knoepp, 1941	7.4
Cameron, O'Rourke & Burt, 1949	10.0
Present material	5.1

possible. Subcutaneous emphysemas are adequately treated with intrapleural suction. Supraclavicular incisions have also been carried out to empty the emphysema. In two cases thoracotomy was performed, in one with repositioning and osteo-suturing of the ribs and in the other with evacuation of coagula on account of major intrathoracic hemorrhage. In two cases laparotomy was performed on account of suspected abdominal injury, but without positive finds. In about 15 % of cases there was hematuria, thus indicating the importance of sediment controls in connection with thoracic injuries. Where the finds are positive, urography should be carried out if the patient's state permits of this.

The mortality was 5.1 %. Some comparative figures for mortality are given in Table 6.

The treatment of thoracic injuries with rib fractures without any clinically observable effect on the lung function scarcely requires any special arrangements. Application of the therapeutic views as to the treatment advanced by Chamberlain & Daniels (1951) gives good results in the great majority of cases, even with limited hospital resources. Their principles may be summarized as follows: free respiratory passage, expanded and air-filled lung, controlled bleeding, combatted pain and immobilization. We do not intend to dwell on these injuries, but prefer to discuss the treatment of the severest thoracic injuries, where newer methods have been adopted with promising results. The above-mentioned principles (Chamberlain *et al.*) are of course valid here too.

Discussion of tracheotomy and respirator treatment

The understanding of respiratory physiology, increasing in the course of the years, led surprisingly late to practical applications in accident surgery. Intubation and positive-pressure respiration had been practised for a long time within the walls of the operating department, but in the accidents department they were reserved for the unconscious. The treatment of persons with severe thoracic injuries was rather restricted to the external stabilization of the thoracic wall to facilitate the patient's own respiration. Analgesics and intercostal blockades were administered with the same purpose and where the injuries were less extensive this treatment was adequate. In bad thorax cases, however, the lung function is so impaired that the patient is not able to get rid of the carbon dioxide produced, even if for longer or shorter periods he can be tolerably well supplied with oxygen. In every case of thoracic injury with affected general condition, multiple rib fractures, paradoxical respiration, disquiet, pallor and cyanosis, ineffective coughing, gurgling bronchi, and recourse to the auxiliary respiratory musculature, one may easily suspect carbon-dioxide retention. The diagnosis

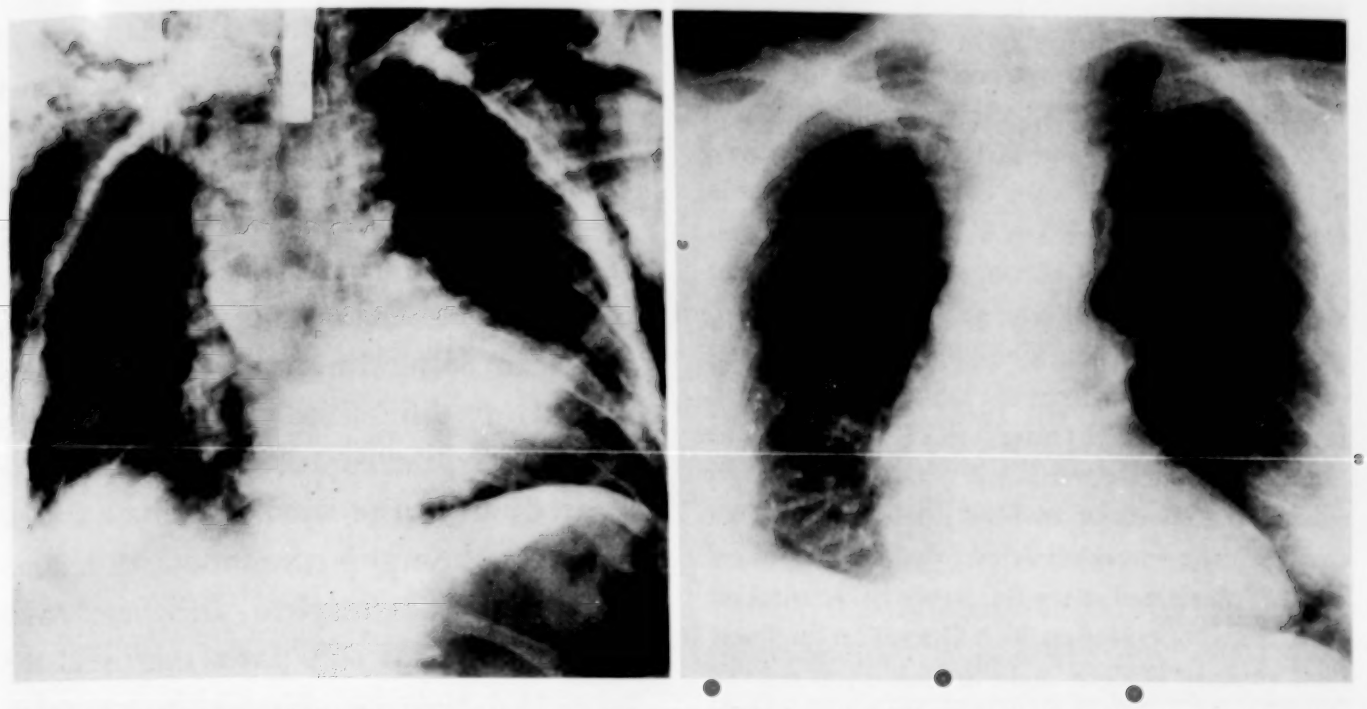


FIG. 4. Appearance of the X-ray picture on day of admission and 5 months later in a case of severe crushing injury to the chest (case report 990204/58).

connection with the fever resulted in inadequate excretion of carbon dioxide through the properly functioning right lung and anoxia. The picture of carbon-dioxide poisoning and pulmonary edema developed and was instantly counteracted with respirator treatment. In the second case there was considerable subcutaneous emphysema due to pneumothorax which could not be diagnosed by X-ray and was revealed only by exploratory puncture. Despite respirator, unsatisfactory respiratory function, probably on account of the considerable pulmonary leak which reduced the ventilatory capacity of the right lung. Only after prolonged drainage treatment did the air-leak heal and the patient's condition improve. Fig. 4 shows the appearance of the X-ray before and after the treatment.

Respirator treatment has in our material been given in twelve cases. Five of these died.

From the account of the fatal cases it appears that the respirator treatment as such did not have great possibilities of affecting the issue (cases 9, 11, 13, 14 and 15).

B. Traumatic Bronchial Rupture

There are two cases in this group. A brief account of these is given below.

1. A 5-year-old boy in January, 1945, was run over by a 3-ton lorry and admitted to hospital with seriously affected general condition, shock, multiple rib fractures, bilateral pneumothorax and mediastinal and subcutaneous emphysema. X-ray examination five days later showed a shadow behind the heart and decreasing emphysema. Good improvement and was sent home. Troubled with shortness of breath and therefore readmitted to hospital. X-ray examination now revealed an opacity of the left hemi-thorax and dislocation of the mediastinum to the left. There was no change in this X-ray picture for a long time. The general condition was good but the patient was still short of breath. Bronchography 10 months after the accident showed total occlusion of left main bronchus about 1 cm distally from carina. Operation verified the X-ray finding.

tainly reveal a pneumothorax. When these measures have been taken, the patient is connected to the respirator. If possible, samples should be taken for a determination of the pH of the blood, pCO_2 and standard bicarbonate before and after connecting the patient to the respirator. If arterial samples are taken, it is also possible to get the value of the oxygen saturation of the blood. Dilatation of the stomach is common in connection with thoracic injuries and may be counteracted with an indwelling tube. By way of illustrating this form of treatment, two cases may here be related.

Interesting and illustrative respirator cases

1. 301209/57. 27-year-old man. On 26.10 skidded on motor bicycle and was precipitated under a lorry, whose back wheel partly passed over the left half of the thorax. Struck his head and was unconscious for a moment but immediately came to. Admitted to Clinic for Thoracic Surgery. Survey of abdomen showed no free gas or fluid in abdomen. Moderate subcutaneous emphysema over left half of thorax. X-ray examination of lungs and thorax revealed fractures of 3rd to 9th ribs inclusive on left side. Left hemo- and pneumothorax. Infiltration in parenchyma of left lung. Fracture through manubrium sterni. The patient was affected by pain but not in state of shock and showed no signs of respiratory failure. Tracheotomy therefore not performed but analgesic treatment under careful supervision. Good improvement. During the next two days the fluid in the left pleura increased and air-content diminished in left lung. Simultaneous rise in temperature to 39°C. on 29.10, when patient suddenly underwent worsening with stupor, dyspnea and bad colour. He was tracheotomized and put in respirator. Astonishingly quick improvement as soon as mechanical respiration was started. Copious secretion from respiratory passages. Repeated pleural punctures. Progressive improvement. Could be definitively taken from respirator on 7.11. Discharged on 20.11 in good general condition. Working full time again on 1.2.58.

2. 990204/58. 58-year-old man. Was leaning against iron railing on 17.3.58 when a 2.5-ton bulldozer rolled against him. Was pressed so hard against the railing that the latter was broken and he fell into a pit 5 meters deep. Admitted to another hospital in seriously affected state with respiratory difficulties, shock and subcutaneous emphysema. Paradoxical respiration. Was at once given Macrodex and then blood. He was given positive-pressure respiration with mask and bag and dislocation of left humerus was reduced. During the positive-pressure respiration the subcutaneous emphysema increased. Was transferred to Clinic for Thoracic Surgery where he was at once tracheotomized and put in respirator. X-ray revealed numerous right-sided rib fractures, fracture of clavicle but *no pneumothorax.* Another X-ray examination a couple of hours later still showed no pneumothorax. The subcutaneous emphysema increased further, the blood pressure rose to 200 mm Hg and pulse rate increased to 110/min. The pleura on the right side was then punctured and a considerable amount of air sucked out. Intercostal drainage accordingly established. Blood pressure went back to 115. There was considerable leakage from the right lung into the pleural cavity. 17 l/min. was given in the respirator but only between 9 and 10 liters was returned. After establishment of permanent pleural drainage progressive and surprising improvement. Lay with respirator from 17.3 till 31.3. Had fever between 38° and 39°C during the first week in spite of antibiotics. X-ray pictures of lungs showed clearing up. The pleural drainage had to be retained until 1.4 on account of considerable air-leak. Despite moistening in the tracheal cannula, quite a number of troublesome crusta formations in cannula and trachea. Strong suction brought up fibrin clots constituting a respiratory hindrance. After removal of cannula and when patient had been up for a week, he could be discharged in good general condition on 29.4.58.

In the first case there were no observable signs of respiratory failure. Notwithstanding this, there was poor ventilation of the left lung with atelectasis and fever. The increased metabolism in

injury will then be diagnosed in the period immediately following this. Small bronchial ruptures are probably able to heal without impairment of function. If operation is indicated, it should be performed early and in any case an attempt at reconstruction should be made; pneumonectomy can only be defended in cases in which the blood vessels of the lung are so badly damaged that perfusion of the lung is jeopardized. Case 1 provides an illustration of the difficulty of arriving at a correct diagnosis. The case was at first judged to be one of left-sided chylothorax, and 1 month after the accident the left half of the thorax was no longer leaking and the mediastinum displaced to the left. There was no change and the patient was in good condition until 10 months later, when total occlusion of the left main bronchus was verified bronchographically. That pneumonectomy was performed on account of the bronchial stenosis and that no attempt was made to anastomose the bronchus must be seen against the background of the view concerning treatment of these injuries that was current at the beginning of the 1940's. The first successful bronchial resection was performed as late as 1948 by Griffith.

Case 2 is an illustration of the possibility of making an end-to-end anastomosis of the totally ruptured bronchus despite the fact that atelectasis and non-functioning of the lung had persisted for 5 months. The lung expanded completely postoperatively and no bronchiectasis had developed, which could be established with bronchography.

Even if a long time has elapsed between injury and diagnosis, an attempt to restore continuity in the bronchus should always be made.

C. Traumatic Aortic Injuries

There are two cases in this group, one from 1957 and the other from 1958. Both were men, 35 and 33 years old respectively. In both cases the injury had been sustained by driving off the road and in both cases the victim was driving and had been flung against the steering wheel. When the immediate sequel after the injuries had been overcome, there was in the one case no other subjective trouble than a humming noise from the thorax synchronously with the pulse. The other patient was troubled with an irritating hacking cough. In both cases it was possible with aortography to show an aneurysm the size of an orange in the thoracic aorta just after the branching off of the subclavian artery. The 1957 case was operated upon with resection of the aneurysm and suturing of the aorta and the 1958 case with aorta resection and the insertion of a graft with end-to-end suture. In neither case were there any complications in the postoperative period. Fig. 5 shows aortography of the last-mentioned case before and after operation.

Discussion

Ruptures of the aorta are probably a more common result of non-penetrating chest injuries than has hitherto been supposed. As about 15 per cent of those sustaining these injuries survive the accident itself, it is important that the condition should be recognized so that early surgical treatment may be undertaken.

Left-sided pneumonectomy performed. Postoperative period without complications and the boy discharged on 23.12.45.

2. 639/52. 7-year-old girl. On 1.8.51 received a blow in scapular tract of left half of thorax from handle of wheelbarrow. Admitted to hospital with extensive subcutaneous emphysema, right-sided pneumothorax with mediastinal displacement to the left. The following day regression of emphysema. Frequent lung controls showed totally collapsed right lung. On 26.11.51 was sent home with unchanged X-ray picture of lung. As she showed shortness of breath and cyanosis on exertion, she was readmitted to same hospital on 20.12. Transferred to the Sabbatsberg Hospital on 16.1.52 and operated on 30.1. Operation disclosed total rupture of right main bronchus just next to the branching off of bronchus of superior lobe. Both bronchial stumps healed. After excision of cicatrized tissue the stumps were sewn end to end. When the bronchial tree had been sucked clean, the lung could immediately be filled with air. No complications in postoperative period. Repeated X-ray controls showed good air-content in right lung which had expanded all the way to the thoracic wall. Discharged on 27.3.52.

Discussion

Traumatic rupture of the main bronchi is a rather rare complication of thoracic injuries. Bronchial rupture is often combined with other injuries to the intrapleural structures. One may therefore suspect that the immediate mortality is high. As the injury is easily accessible by surgical treatment, it is important that the diagnosis should be made early. The accident is commonly a severe trauma to the thorax, e.g. lorry wheel over the chest (case 1) and more rarely a blow on the thorax. The site of the bronchial rupture is as a rule localized to one of the main bronchi about 1 cm from the bifurcation. It has been asserted that the mechanism for the injury is either a compression of the bronchus between the spine and the soft thoracic wall or the increased intrabronchial pressure arising in consequence of the patient's closing the glottis and holding his breath before the expected trauma. If the bronchial rupture is more peripheral, then the pleural symptoms in the form of tension-pneumothorax with respiratory difficulties may predominate. If, however, the rupture is more centrally located, then the mediastinal and subcutaneous emphysema may dominate the symptom complex. In these cases the mediastinal soft parts may seal the bronchial rupture. Mediastinal emphysema must thus always be regarded as a symptom of bronchial or esophageal rupture and the patient treated accordingly until the diagnosis is verified. Patients who survive the acute injury and in whom the bronchial rupture has been sealed develop a non-functioning atelectatic lung. The diagnosis is made with X-ray examination and it has been pointed out by Norlin (1955) that in cases with thoracic injuries with pneumothorax and mediastinal emphysema sufficiently penetrating films should be taken to permit a detailed study of the trachea and main bronchi. In this way an exact diagnosis is in the majority of cases possible at an early stage. If X-ray is not able to show the bronchial rupture during the acute stage, it becomes necessary to carry out bronchoscopy. The difficulty of combatting a pneumothorax owing to the magnitude of the air-leak may sometimes necessitate exploratory thoracotomy, whereupon the bronchial rupture is disclosed. A conservative treatment may, on the other hand, be sufficient as early treatment and the

later, or in whom the developed aneurysm is observable in connection with a routine X-ray. It is therefore extremely important that persons who have been exposed to accidents of this kind should be made the subject of routine examinations for a sufficient time after the trauma so that the diagnosis is not neglected. Pains in the chest, hoarseness, coughing, respiratory difficulties, dysphagia and hemoptysis are important symptoms indicating the development of a mediastinal hematoma. The diagnosis is roentgenological and aortography reveals the site of the rupture. Even if there are advocates for conservative treatment of aortic aneurysm, surgical treatment strikes us as necessary on account of the grave risk of rupture, even though operative mortality is relatively high. Experience has shown, however, that the operative mortality is already declining. The treatment is therefore resection of the aneurysm and the restoration of continuity in the aorta with a graft if necessary. The higher in the aorta the aneurysm is, the greater will be the technical problems confronting the operator. With a very highly placed aneurysm one cannot find room for a clamp forceps without at the same time closing the carotids, which cannot be tolerated without special arrangements such as hypothermia or temporary shunts. In both of our cases the clamping of the aorta during the period that was required for the completion of the suturing was rendered possible by hypothermia to 30°C.

D. Traumatic Myocardial Injuries

There is one case in this group, no. 440519/58. A 14-year-old boy while playing basket-ball was bumped against the wall in the gymnasium on 17.10.58. Struck left side of chest and abdomen. On account of tenderness and ache in abdomen and increasing shortness of breath, fatigue and palpitations was admitted to hospital on 22.10 for observation on suspicion of intraperitoneal hemorrhage. X-ray showed a general enlargement of the heart and pronounced pulmonary stasis. Gradual worsening of the general condition. Transferred to medical department where on 24.10 renewed X-ray examination revealed a further enlargement of the heart. Venous pressure 16 cm. Puncture of pericardium for suspected hemopericardium yielded 35 cc of dark blood. The punctate coagulated. After puncture a chafing sound was heard over cor. During this stay in hospital, fever about 38°C. As patient's condition grew still worse and the diagnosis hemopericardium seemed probable, he was on 24.10 flown to the Clinic for Thoracic Surgery. On admission his general condition was strongly affected with violent dyspnea, tachycardia, cyanosis and swollen liver. X-ray revealed enlarged, rounded heart and pulmonary stasis. As the state was diagnosed as cardiac tamponade, it was decided to perform a pericardiostomy and the narcosis was begun. In connection with the intubation the patient's heart stopped beating. Immediate incision and heart massage, whereupon the heart started beating again. The pericardium contained only a small amount of fluid. The heart was extremely large and the anterior wall stiff, pale and with very small movements. Suture of the incision. Tracheotomy and respirator. Blood pressure of 70–80 mm Hg could be maintained only with noradrenalin, blood transfusions and hydrocortisone. Unconscious with left-sided hemiplegia and violent electrocardiographically recorded dysrhythmias of various kinds. Was given pronestyl. Removed from respirator on 3.11 and was thereafter able to ventilate himself. Regular pulse without deficit only after 1.12. Had eaten and drunk since 24.11. Gradually became clearer and could start talking. Blind. Three months after the operation vision returned, as did also the power of movement in the left half of the body. Was able to get up and walk and could see to read. Still an inmate of local hospital, from which reports of further improvement have been received. X-ray pictures and ECG shown in Figs. 6 and 7.

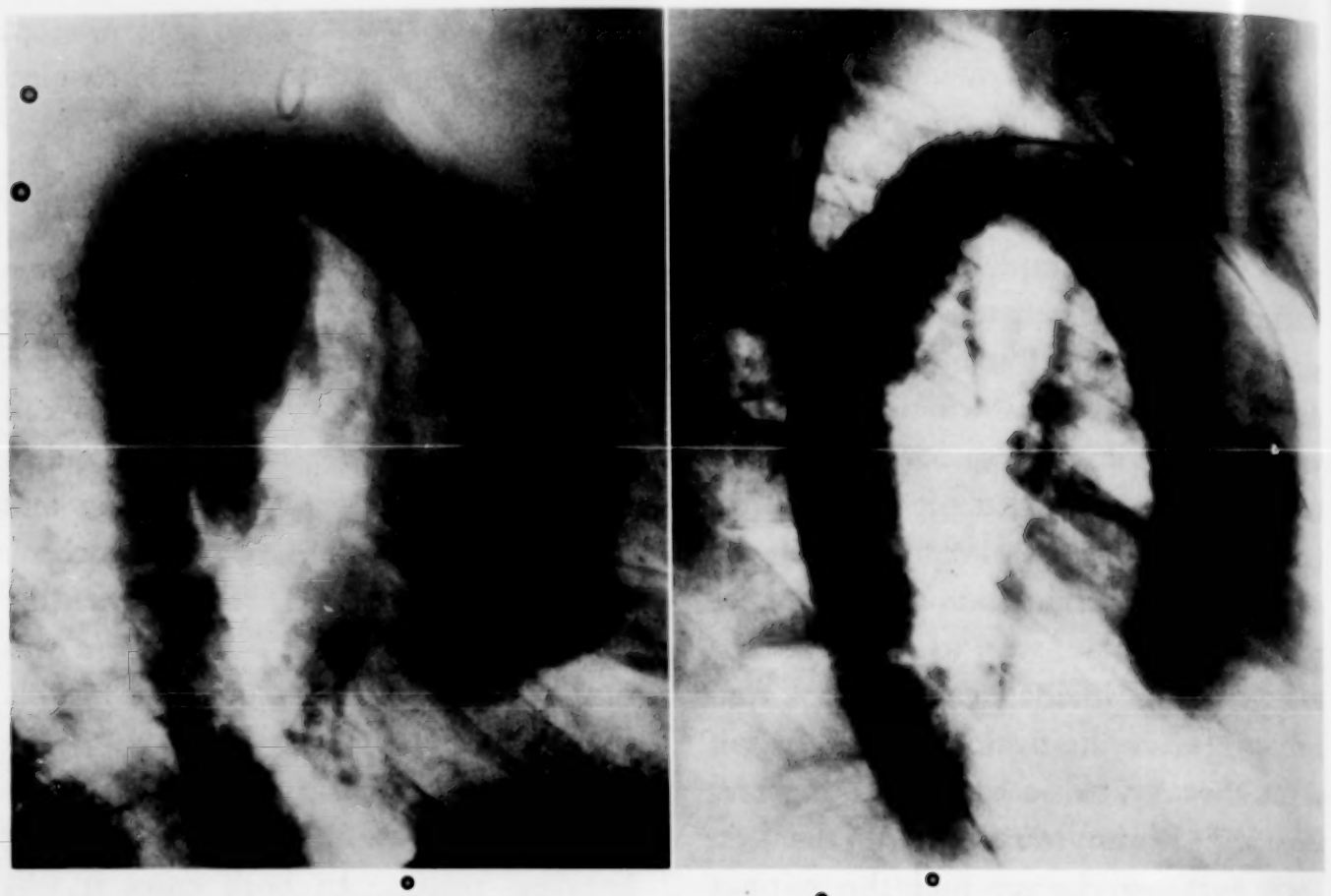


FIG. 5. Preoperative and postoperative aortography in a case of traumatic aortic aneurysm.

According to Parmley, Mattingly, Manion & Jahnke (1958), 67 % of these injuries are caused by motor-car accidents, and since the number of injuries due to traffic accidents is constantly increasing it appears probable to us that the aneurysm will come to play a still more important role than hitherto. The forces which are able to cause a rupture of the aorta are the same as those connected with other non-penetrating injuries to the chest, viz. direct and indirect. These forces act upon the thoracic aorta with a predilection for certain sites. One of these is the descending aorta immediately distal to the subclavian artery. It is surprising that anyone survives the actual aortic rupture, and this must be due to that fact that the rupture does not involve all the layers of the wall or that a hematoma is formed in the mediastinal tissues, thus preventing the immediate rupture of the vessel. In the sequel the hematoma grows mediastinally and the patient is the whole time threatened with rupture of the hematoma with immediate death as a result. While the hematoma is growing, it may exert pressure upon different mediastinal structures which may provoke symptoms from which the condition may be suspected. Thus, for example, the case from 1958 had an irritating cough owing to the pressure exerted by the hematoma on the left main bronchus and invasion in the left inferior lobe. Symptoms indicating these serious injuries may appear both hours and days after the accident; but there are also others who, after surviving the period immediately following the accident, do not manifest any symptoms until the aortic aneurysm bursts weeks or months

traumatic hemopericardium. The prognosis for this injury must be regarded as serious, but it varies of course with the extent of the injury. Samson has reported 31 % mortality. The treatment is entirely symptomatic.

In our particular case the symptom complex was dominated by cardiac insufficiency. The X-ray picture with the large round heart and the previous pericardiac puncture resulting in temporary improvement both supported the assumption of cardiac tamponade. The contents of the pericardium were adjudged to be in part coagulated blood, so that further puncture was considered unnecessary, since it would not have been possible to evacuate the coagulated blood completely by this means. The evacuation of the coagula was deemed possible only through pericardiotomy. Owing to the patient's bad condition, we were prepared for cardiac complication in connection with the induction of narcosis. When the heart stopped, it was thus possible to perform immediate thoracotomy and apply massage until it resumed its function. When the heart was exposed, the anterior and left walls were found to be changed in appearance. The colour was pale brown with yellowish patches. The heart was strikingly large and the visible parts of the left ventricle were scarcely performing any contractions. After the operation the patient was put in the respirator and the blood pressure was maintained at about 70–80 mm Hg with the help of blood transfusions and noradrenalin drip. Although we were prepared for the cessation of the heart's activity, so that thoracotomy could be performed immediately, the patient sustained an anoxemic injury to the central nervous system which was not restored until after the lapse of 3 months. The picture of the disease was interpreted as a traumatic myocardiac injury. Owing to the difficulty of interpreting the picture, the paticnt had the added strain of a thoracotomy. Despite the operation, the patient survived, and the happy issue is to a large extent to be ascribed to the anti-shock and respirator treatment. In Fig. 6 may be seen the appearance of the heart before the operation and 3 months later.

Dr. Sture Bevegård from our physiological laboratory summarizes the ECG changes as follows: From 25.10 and the immediately succeeding days the ECG series shows supraventricular tachycardia with development of impulses from varying auricular foci. At intervals relatively frequent ventricular extra systoles. (Fig 7*a*). The frequency varies from about 130/min. to about 170/min. The first ECG recording with 5 precordial leads (CR-leads) shows right ventricular pattern in both extremity leads and all precordial leads. Only in lead a VL is there any indication of left ventricular pattern. The amplitude of QRS is very low in the leads CR_{5-7} (normally corresponding to the left ventricle). In lead CR_7 the initial complex is split up as it is in connection with intraventricular conduction obstacle. Furthermore, two-phase T-waves as in connection with general myocardiac injury (Fig. 7*b*).

In the ECG recording as from 29.10 the initial complex has been partly normalized and the left ventricular pattern is found in the lead CR_7. As from 31.10 there are at intervals recordings of ordinary sinus rhythm and at intervals, as previously, development of impulses from varying auricular foci with series of extra auricular systoles and varying frequency of extra ventricular systoles. In December essential normalization of the initial complex, but remanent signs of myocardiac affection which appear to be localized on the whole to the apex region (Fig. 7*c*).

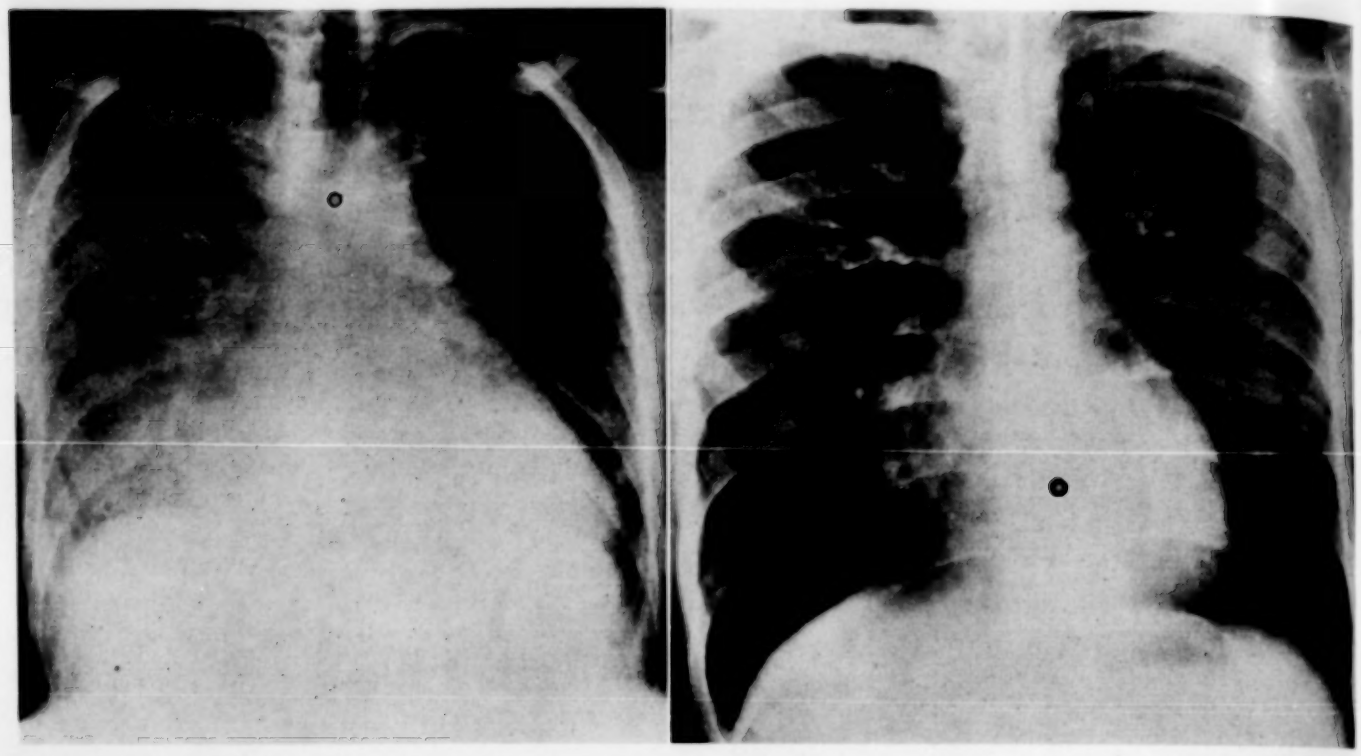


FIG. 6. Appearance of the X-ray picture on day of admission and 3 months after operation in a case traumatic myocardiac injury (case report 440519/58).

Discussion

Contusion of the heart with subcutaneous ruptures of the myocardium is a clinically relatively unequivocal concept. The case is otherwise with the neither macroscopically nor microscopically unobjectionable changes that may appear in connection with subcutaneous thoracic injuries and are referred to as commotio cordis. There is a floating line of demarcation between these changes and those in which it is possible to show definite injuries to the myocardium and which are generally referred to as contusio cordis. As in the case of commotio and contusio cerebri there is here probably only a difference of degree but not of kind. Trauma of the anterior thoracic wall is probably a common cause, e.g. traumata from being flung against the steering wheel in car accidents, though innumerable other traumata to the thorax, both direct and indirect, have been reported as the cause (Warburg, 1938; Sournia, 1958; Derra, 1959). Kissane considers that 15 % of all deaths due to non-penetrating injuries to the chest are due to heart injury.

The symptoms often appear immediately, but in a number of cases there is a symptom-free interval of several days. The symptom complex is dominated by signs of cardiac insufficiency with tachycardia, hypotonia, dyspnea, cyanosis and cerebrally affected status. Electrocardiographically it is possible to observe, inter alia, every conceivable dysrhythmia. The condition is hard to distinguish from other cardiac affections and may often present the appearance of hemopericardium, cardiac infarct or acute myocarditis, especially as the trauma may have been only slight and followed by a symptom-free interval.

The enlargement of the heart observed on the X-ray may be confusingly like a

tained the injuries in attempts at suicide. One case occurred in each of the years 1942, 1945, 1947, 1949, 1951 and 1958, and 4 cases occurred during 1957. The age varied between 18 and 43 years and the period of hospitalization between 1 and 27 days.

There was hemothorax in 10 cases, pneumothorax in 8 and subcutaneous emphysema in one case.

Two cases required immediate operation on account of hemorrhage. Four cases were treated with repeated pleural punctures or permanent pleural drainage. The remaining 4 could be treated conservatively. Antibiotics were given in 8 cases. There were no deaths in this group.

Discussion

The penetrating thoracic injury is for obvious reasons associated with war-like actions. Experience of these war wounds is therefore taken as the basis for their treatment in peace-time. The surgeons who worked in the great theatres of war during the last world war have the widest experience of these injuries. They report a reduction in the mortality from 25 % during the first world war to 6 % during the second.

The principles of treatment are on the whole the same as those described for crushing injuries (see page 9). This implies that the respiratory passages must be kept free through tracheo-bronchial aspiration if the patient himself cannot satisfactorily expectorate. This may be done either by bronchoscopy or, if necessary, by tracheotomy. The patient must be kept free of pain, e.g. through intercostal blockade. In cases with penetrating thoracic injuries there is the risk of infection in the opened hemopneumothoracic cavity. Also tension pneumothorax and subcutaneous emphysema may occur. The best and most effective treatment to obviate impairment of the lung function due to empyema and pleural scar is early and thorough aspiration of the pleura. Owing to the risk of contamination, an adequate antibiotic therapy is necessary from the outset. While the majority of penetrating thoracic injuries can in peace-time conditions be treated conservatively, there are nevertheless certain indications for thoracotomy. Continued bleeding from intercostal, mammary or pulmonary vessels calls for exploration. Big wounds with fragments of bone and exposed pleura require exploration and suture and in connection therewith the removal of foreign bodies and the fixation of fragments of rib are probably indicated. Injuries to the lung, on the other hand, do not, provided there is no major hemorrhage, require any other surgical measure than those bringing about early and complete re-expansion of the lung.

In only one of our cases was there an open channel to the pleura through a big wound after a blow with an axe—sucking wound. The wound was explored and the pleura drained. Of the remaining cases only 4 required treatment against hemopneumothorax. Of particular interest is the fact that one of our patients refused treatment and disappeared on the day of admission without anything further being heard of him, and this despite a pneumothorax after being stabbed in the chest.

Many of the cases were attempted suicides.

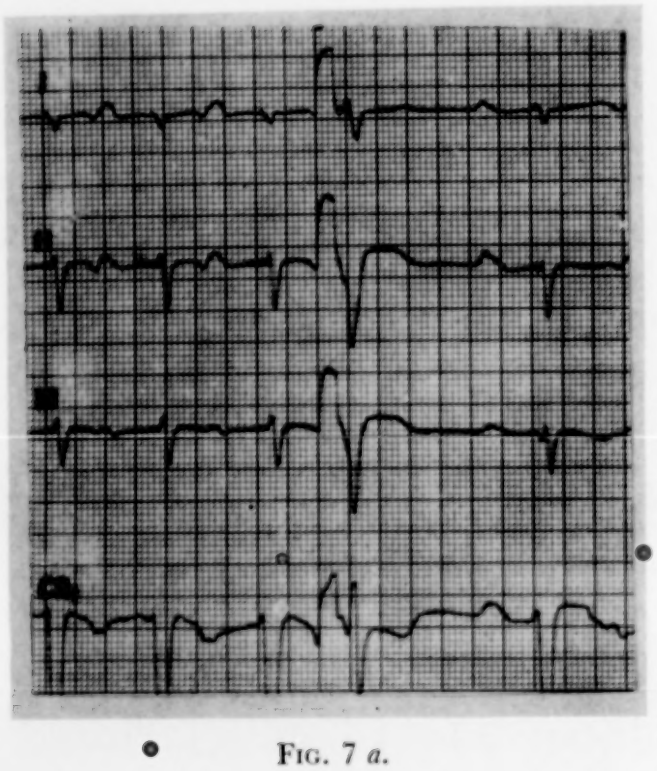


FIG. 7 *a*.

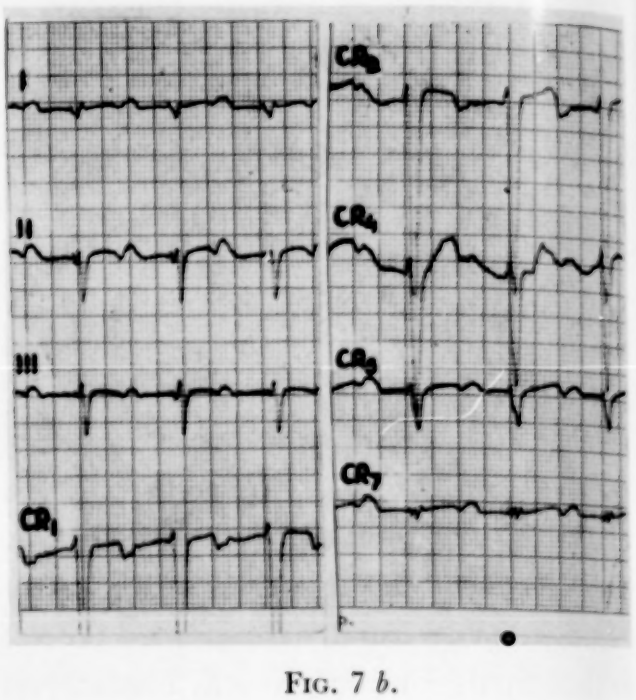


FIG. 7 *b*.

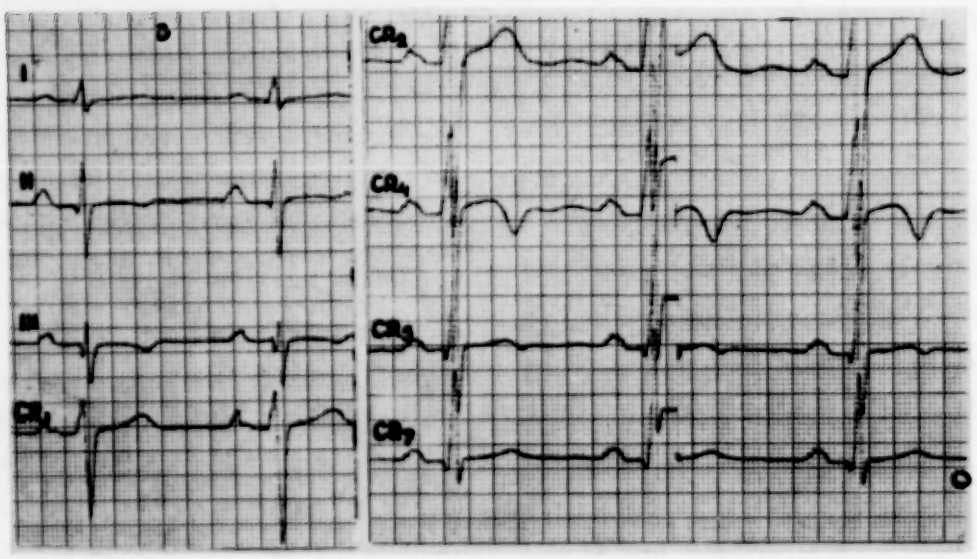


FIG. 7 *c*.

FIG. 7. *a*, *b*, *c*. For explanation see text.

Summarizing, one may say that the ECG series has shown abundant occurrence of both supraventricular and ventricular extra systoles and signs of myocardiac affection later localized to the apical region. In the first days after admission the left ventricle appears from the ECG viewpoint to have manifested very slight activity. After some days, however, signs of electric activity in the left ventricle recur. We find no typical ECG picture for infarctation.

2. PENETRATING INJURIES TO THE CHEST

A. CASES WITH LUNG INJURY

Ten cases are included in this group, 9 men and 1 woman. The injuries were caused in 5 cases by stabbings, in 1 by the stroke of an axe and in 4 cases by rifle or revolver shots. Five patients sus-

sutured and inspection of the pericardium revealed a hematoma the size of a penny in the pericardium to the right of the heart. The patient's condition underwent worsening postoperatively and he died in the picture of a pulmonary edema. Autopsy disclosed a fresh cardiac infarct in the left ventricle, corresponding to the thrombotized and contused right coronary vessel. The only perforating vascular injury was a traumatic aneurysm in the left subclavian artery from the bullet wound. The aneurysm was extirpated and the vessel was sewn end-to-end.

SUMMARY

A material of 313 cases with thoracic injuries from 1938–1958 is analysed. The material includes groups with rib fractures, bronchial rupture, aortic aneurysm, traumatic myocardiac injury and penetrating heart and lung wounds. The mechanism for the mode of infliction of the injuries, the symptomatology and the treatment are briefly discussed for each group of injuries.

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B. Cases with Injury to the Heart or the Great Vessels

Five male cases were treated for such injuries during the period for the investigation, with one case for each of the years 1945, 1948, 1949, 1955 and 1958. Two had bullet injuries, two had knife-wounds and one had injuries from a fall on a long splinter of glass. Two of the patients had injured themselves in attempts at suicide. The age varied between 13 and 43 years and the period of hospitalization between 4 and 66 days. Hemothorax occurred in 3 cases and pneumothorax in 2.

Four of the cases required operation, and the fifth could be treated conservatively. They are briefly described in the discussion. There was one death in the group.

Discussion

These injuries are of a more dramatic nature and survivors from them may be estimated as 15 % according to Parmley *et al.* The immediate consequences of a penetrating heart wound are hemorrhage and cardiac tamponade. Injuries to the pericardium always exist simultaneously with the heart-wound but may also occur without injury to the myocardium. If the injury to the pericardium is slight, the hemorrhage may, if it continues, give rise to cardiac tamponade. A major pericardiac injury allows the bleeding free passage into the thoracic cavity. In cases of hemopericardium pericardiocentesis has been recommended, but this is risky and should be undertaken only if there are signs of cardiac tamponade. Attention has been drawn to the value of conservative treatment in cases of penetrating heart-wounds and only puncture of the pericardium has been undertaken to reduce the cardiac tamponade (Cooley, Dunn, Brockman & DeBakey, 1955). There are, however, certain accepted indications for operation, e.g. symptoms of cardiac tamponade that do not disappear after aspiration, rapid accumulation of the cardiac tamponade and continued hemorrhage outwardly or to the pleura. In the treatment of injuries to the great vessels, on the other hand, there is no justification for the conservative attitude. It is difficult to deal schematically with these cardiac and vascular injuries, and each case must be taken individually with independent judgement. In the course of treatment 30 % of those who have survived the immediate trauma succumb.

The material includes 2 cases with pericardiac injury. In one case there was only the X-ray diagnosis of air in the pericardium and no active measures were called for. Seven days after the infliction of the trauma the second case developed signs of cardiac tamponade and satisfactory aspiration proved impossible. The pericardium was accordingly drained with pericardiostomy. After a further 3 weeks decortication of the heart was performed on account of symptoms of constrictive pericarditis.

One case of a knife-wound in the anterior wall of the right ventricle with rapidly developing symptoms of cardiac tamponade required thoractomy and suture of the perforation in the ventricle.

One case was operated upon on the suspicion of hemorrhage in the right pleura after a pistol shot in the chest. On operation the pulmonary leak was

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From the Departments of Pulmonary Diseases and Pathology, St. Göran's Hospital, Stockholm, Sweden

Cavern Formation in Pulmonary Sarcoidosis

SVEN LÖFGREN and ÅKE G. H. LINDGREN

The occurrence of intrapulmonary cavities in sarcoidosis is a well-known phenomenon which is especially connected with the tendency to fibrosing with the concomitant formation of bullous emphysemas. On the X-ray picture these may sometimes give the appearance of "caverns". Whether genuine caverns can occur in cases of chronic pulmonary sarcoidosis is, however, a matter of divided opinion, and to throw some light upon the question we wish to give an account of the following case.

CLINICAL DATA

The case is that of a woman, E. B., born in 1918. In 1950, when she was 32 years of age, lung changes of sarcoidotic type were observed: bilaterally and symmetrically enlarged hilar lymph nodes, as well as extensive patchy and streaky densities in the parenchyma, mainly in the central parts of the lungs (Fig. 1). No reaction to Mantoux 100 units, either in 1950 or in repeated subsequent tests. In 1952 lupus pernio appeared in an 18-year-old traumatic scar on the cheek: biopsy showed changes compatible with sarcoidosis (cf. Löfgren *et al.* 1955).

In 1950–1952 X-rays of the lungs showed a certain regression of the hilar lymphomas but increasing fibrosing in the parenchyma. From 1952 there was steadily increased fibrosing accompanied by the appearance of local emphysema (Fig. 2). During the period February–April 1956, cortisone therapy was resorted to. This resulted in a considerable subjective improvement and a certain regression of the lung changes. However, this treatment had to be discontinued on account of recurring bronchopneumonias, for which repeated treatments with antibiotics were given (penicillin and tetradecin). From April 1956, X-ray of the lungs showed a cavity at first walnut-sized, afterwards growing to the size of a hen's egg and located centrally in the right upper lobe (Fig. 3).

From May 1956, purulent sputum appeared; it steadily increased in quantity up to about 200 ml daily in November. Bacteriological examination of the sputum showed, in May, a mixed flora of Staphylococcus pyogenes, Hemophilus hemolyticus, Neisseria, pneumococci and alpha streptococci, but no growth of fungi. In connection with the markedly increased amount of sputum in Novem-

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The heart weighs 260 g, enormously dilated on right side. Spleen weighing 320 g with very pronounced chronic congestion. Also congestion in kidneys and liver. In the latter organ may be seen scattered subcapsular white foci the size of peppercorns, whereas no such foci appear on numerous section surfaces. Apart from gallstone the autopsy did not in other respects reveal anything noteworthy.

Also histologically the lungs present the picture of an older and fresher sarcoidosis, with larger and smaller conglomerations or isolated submiliary to miliary epithelioid cell tubercles of varying age, to a large extent more or less transformed into connective tissue and decapsuled. In the fresher foci may be seen an abundance of Langhans' giant cells, a number of them with suspected inclusion bodies. No caseous necroses. The wall of the large cavity in the right lung is made up in part of fibrous connective tissue and in part of an apparently non-specific granulation tissue with dense lymphoplasmoleucocytal cell infiltration. In some places, however, a couple of entirely hyalinized sarcoidotic tubercles

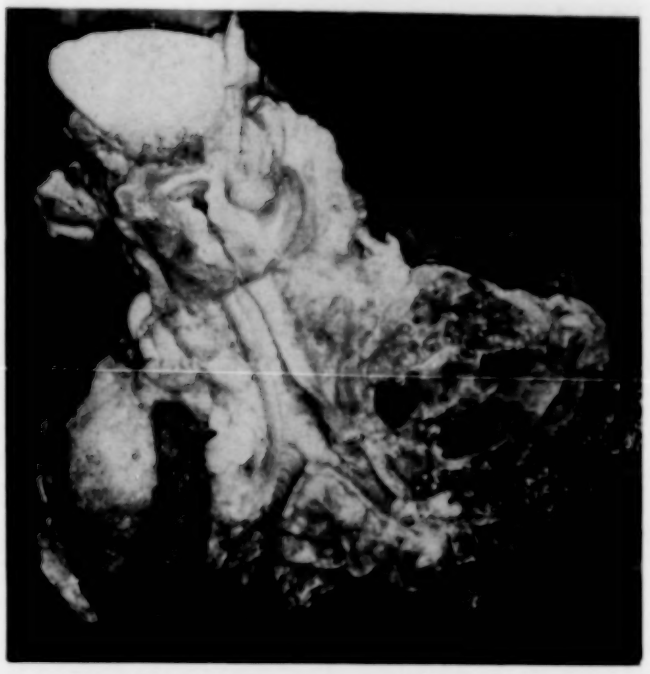


FIG. 4. Frontal section through the lungs with the main bronchi opened (seen from the dorsal side). Located centrally in the right upper lobe a large, relatively smooth-walled cavern in part filled with blood.

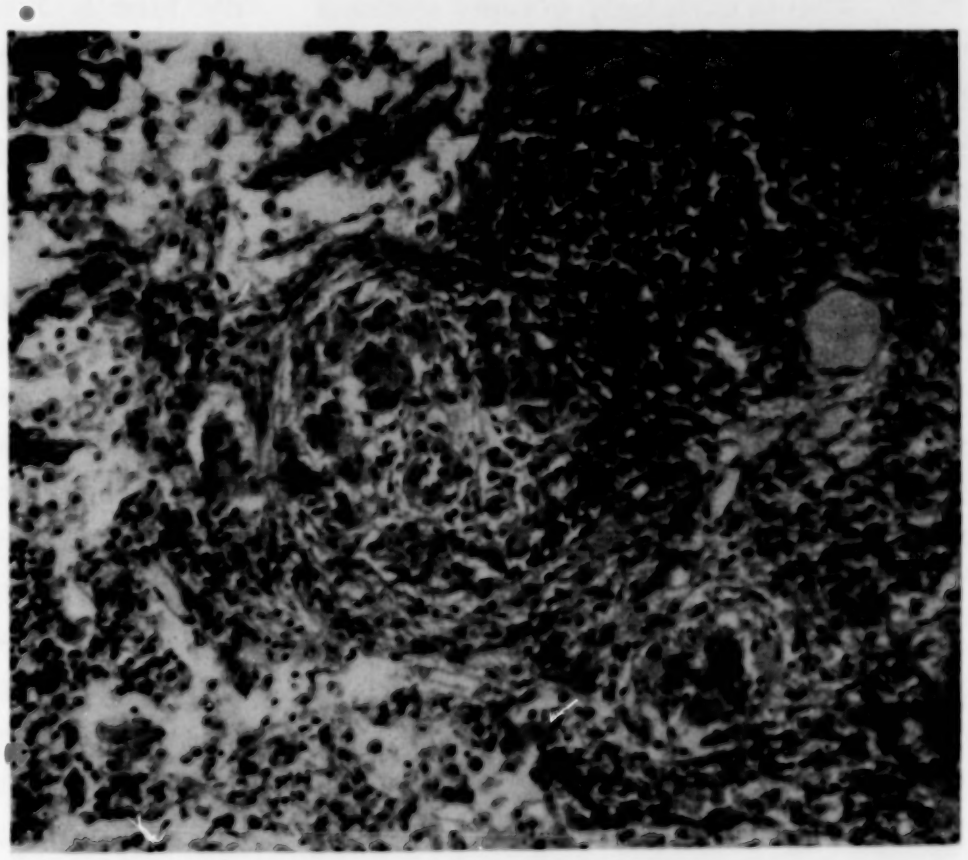


FIG. 5. Sarcoidosis foci in lung. v. Gieson, × 140.

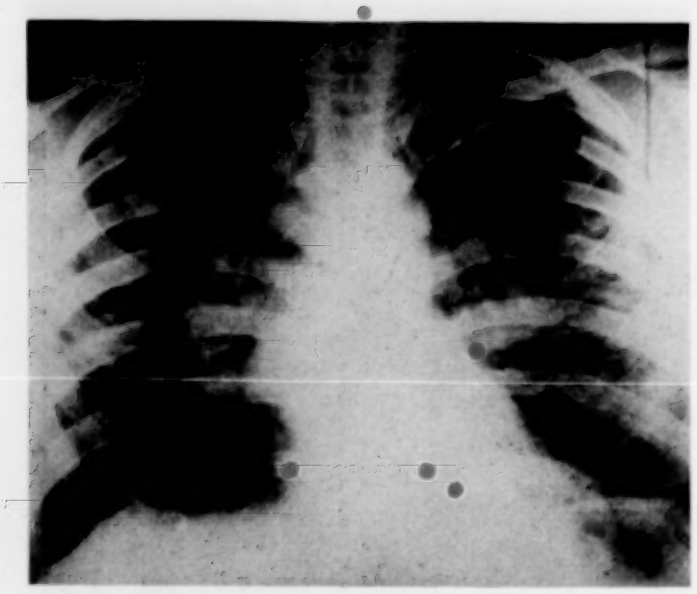


FIG. 1. X-ray of lungs in Feb. 1951: Bilaterally enlarged hilar lymph nodes and patchy and streaky densities in the parenchyma, mainly in the central parts of the lungs.

ber, however, yeast fungi were also repeatedly cultivated from the sputum. Guinea-pig tests and cultivation for the purpose of demonstrating tubercle bacteria from samples of sputum gave negative results.

On December 4th the patient suddenly died owing to copious hemoptysis.

AUTOPSY FINDINGS

Necropsy revealed scattered adhesions between the pleural surfaces on the left

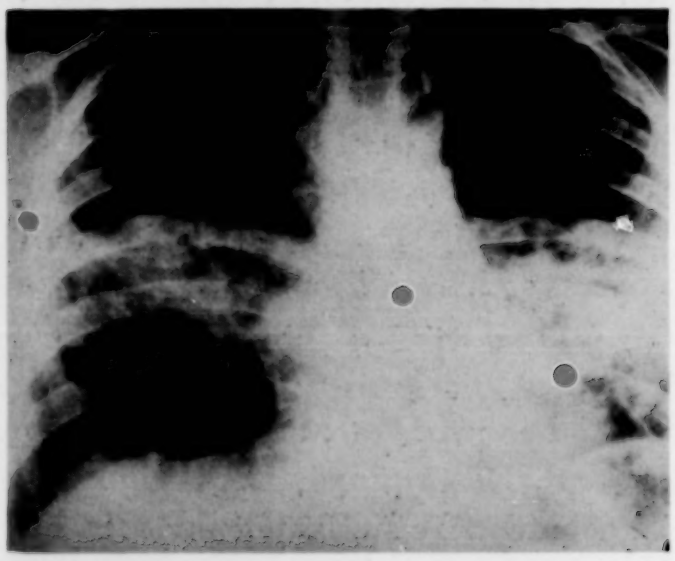


FIG. 2. X-ray of lungs in April 1954: Reduced hilar lymphomas; increased induration with fibrosis and emphysema located centrally in both lungs.

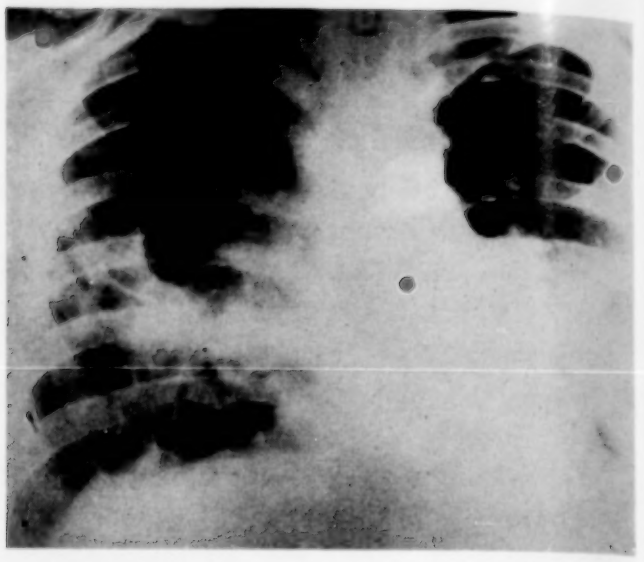


FIG. 3. X-ray of lungs in April 1956: Located centrally in right upper lobe a cavity the size of a large walnut.

side and firm synechia on the right side. The lungs very large, inflated, heavy, reminiscent of cirrhosis of the liver, rather coarse-lobed. A large frontal section through both lungs reveals in their central parts nearest the hilus a dense reticular fibrosis. Furthermore, there are ragged cavities the size of hazel-nuts, rather symmetrically located, on the left side in the top part of the inferior lobe, on the right side basally in the upper lobe. Centrally in the right upper lobe is a blood-filled, moderately smooth-walled cavity the size of a hen's egg. In the peripheral parts of both lungs may be seen an extremely dense, acinously diffused, finely granulated tuberculoid infiltration, with here and there concentration centres of more cicatrized and radiate type in good agreement with the picture of sarcoidosis. In the tracheal bifurcation a very firm, hyaline lymph node the size of a hen's egg. Along the trachea masses of somewhat fresher altered nodes with a typical sarcoidotic appearance. Slight pulmonalis sclerosis but no embolisms or infarcts.

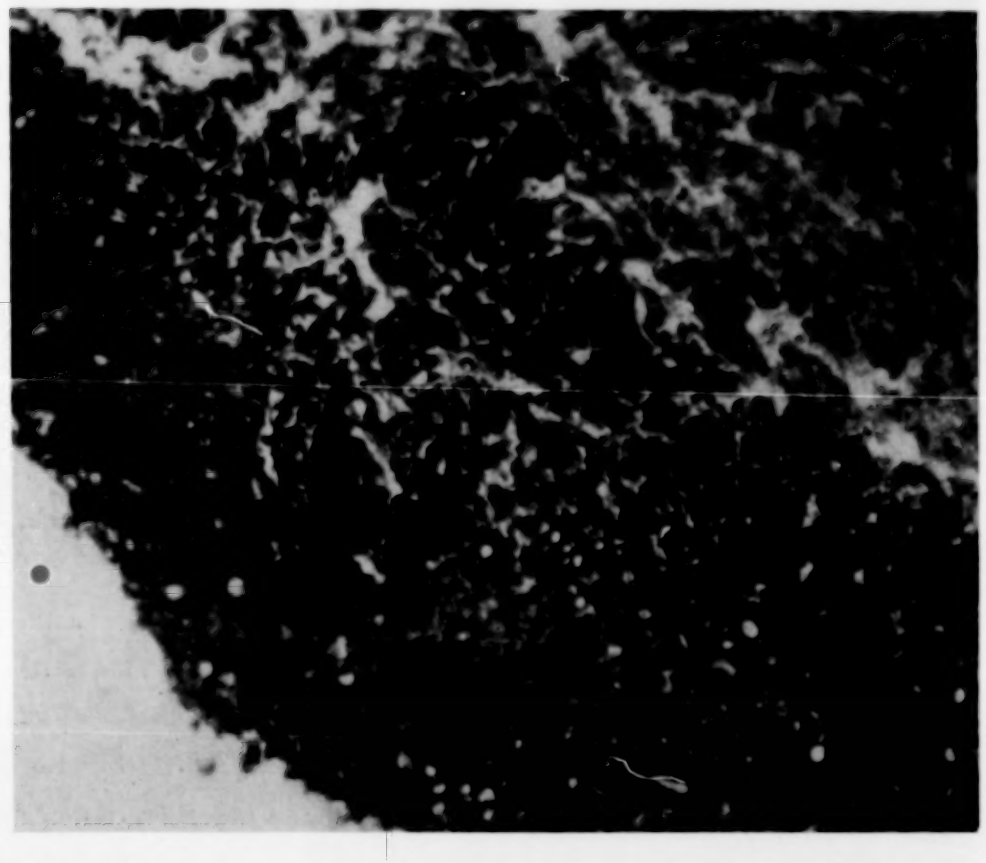


FIG. 7. Fungus hyphae on the surface of necrotic tissue in the cavern wall. v. Gieson, × 140.

logically nor histopathologically were there any signs of tuberculosis; on the other hand, histopathological examination did reveal changes compatible with sarcoidosis. The wall of the large cavity showed in principle the same structure as a chronic cavern on a tuberculous basis.

When discussing the occurrence of genuine caverns in cases of sarcoidosis, it is, of course, first of all necessary to eliminate the possibility of a coexisting classical tuberculosis. Whether one then chooses, in a case of pure sarcoidosis, to refer to thick-walled cavities observed as "caverns" or lung abscesses is a question of definition. If one defines the term "cavern" as a cavity pathognomonic of tuberculosis, it is, of course—provided that sarcoidosis is interpreted as a disease distinct from tuberculosis—not legitimate to call the cavities in question caverns. If, on the other hand, one considers the essential element of the concept "cavern" to be a cavity with a more or less thick, fibrous wall, then it is logical to refer also to the cavity observed in our case as a cavern. Uehlinger, for example, does not hesitate to designate the cavities observed in his three cases as caverns.

As regards the pathogenesis, secondary infection probably plays a decisive role in the origin of sarcoid lung cavities (cf. Scadding 1950). It is in this connection of interest to point out that in the cases described by Adamson *et al.* as well as in that observed by us there was infection by yeast fungi, probably favoured by intensive antibiotic therapy.

SUMMARY

1. Cavitation in a case of chronic pulmonary sarcoidosis is described. The macroscopic and microscopic structure of the cavity justifies its designation as a cavern.

2. Secondary infection, especially fungus infection, is advanced as a probable pathogenetic factor for the cavern formation in cases of pulmonary sarcoidosis.



FIG. 6. The wall of the large cavern with connective tissue and non-specific granulation tissue (above the crack), with necrotic tissue (below the crack). v. Gieson, ×40.

are to be seen nearest the lumen. To the wall of the cavity adhere necrotic masses of tissue and enormous quantities of fungus hyphae, matted together and red in PAS-stained sections.

The large lymph node in the tracheal bifurcation is extremely densely studded with older and fresher tubercles, the former to a large extent transformed into hyaline fibrous matter, the latter with large giant cells of the Langhans type. In places may be seen also large coherent rind-like masses of connective tissue.

In the spleen and liver sparsely scattered conglomerate tubercles with giant cells.

Tubercle bacilli staining negative in sections from the lungs, tracheal lymph nodes, spleen and liver.

DISCUSSION

Roentgenological lung changes in cases of sarcoidosis indicating cavitation were reported earlier by Salvesen (1935), Tice & Sweany (1941), Bernstein & Sussman (1945), Pruvost & Depierre (1946), Ustvedt (1948), Scadding (1950), Uehlinger (1955), and Adamson *et al.* (1959). Autopsy findings of pulmonal cavities with fibrous wall were described by Tice & Sweany (one case), Ustvedt (one case), Uehlinger (three cases) and Adamson *et al.* (two cases). For the discussion of the problem here in question the autopsy findings are of course of more decisive importance than the clinical observation alone.

In the case of chronic pulmonary sarcoidosis described by us the roentgenological examination had revealed a large cavity located centrally in the right upper lobe. To this corresponded the autopsy finding of a relatively thick-walled cavity with smooth walls and the size of a hen's egg. The autopsy also revealed a couple of ragged cavities the size of hazel-nuts and symmetrically located in both lungs. Neither bacterio-

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From the Clinic of Thoracic Surgery, University Hospital, Helsinki, Finland

Solitary Pulmonary Tumours

Based on an Eleven-Year Study of 200 Cases

O. Peräsalo and P. Tala

The solitary pulmonary tumour, the "coin" lesion, may be defined as a parenchymal density which shows up as a peripheral and circumscribed lesion on the chest X-ray. It has presented a serious problem to clinicians since it may signify either an extremely malignant or a benign condition.

The first solitary pulmonary tumour was described in 1883 by Chiari; it was a peripheral chondroma. Graham introduced surgical treatment in 1925 by removing a circumscribed peripheral tuberculoma by thoracotomy. The first series of resected solitary pulmonary tumours was reported by Graham & Singer in 1936. In 1942 Alexander defended thoracotomy as the only realistic method of correctly diagnosing a solitary pulmonary tumour.

A glance at the literature shows that several extensive series have been reported, dealing with different pathological conditions. Effler *et al.* (1948) discussed the solitary lung tumours in conjunction with a study of 24 cases, O'Brien *et al.* (1948) reported on 21 cases, Husfeldt *et al.* (1950) on 24 cases, Hood *et al.* (1953) on 156 cases, Deans (1953) on 76 cases, Meckstroth *et al.* (1954) on 70 cases, Wilkins (1955) on 77 cases, and Ford *et al.* (1956) on 124 cases—to mention only the most considerable series. The largest series of all, and perhaps the one that has been dealt with in greatest detail, comprised 215 cases reported by Davis *et al.* in 1956 following on their study of 40 cases in 1947. They surveyed the entire previous material reported in the literature, altogether 1203 cases, and tabulated the various lesions on a percentage basis.

During the 11-year period 1948–1958 the Clinic of Thoracic Surgery at the Helsinki University Hospital treated cases of lung tumour of which 200 should be referable to solitary lung tumours. Surgery was the main method of treatment.

The solitary lung tumours are comparatively common, they are often entirely asymptomatic, being detected solely by chance, and have frequently proved malignant, in which case the only recourse is to remove the tumour surgically. We therefore considered it would be of value to analyse the material in respect to type of tumour, malignity

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tiated carcinomas, 27 adenocarcinomas and 2 bronchiolar carcinomas.

Of the two cases of lymphoma one was classified as malignant lymphogranulomatosis. Both were round in form and 3.5 × 3.5 cm in size, and both were encountered in the left upper lobe of women 43 years of age. Both cases were discovered by chance during X-ray examination. One case was treated by pneumectomy, the other, lymphogranulomatosis, by enucleation of the tumour.

The solitary bronchial adenomas were encountered in two women and one man. Two of them had had hemoptysis—and the tumours could be verified bronchoscopically and histologically. Both were sinistral, one in the upper and one in the lower lobe. The third, asymptomatic adenoma, was situated in the right lower lobe.

Of the nine cases of primary sarcoma seven were male and two female. Four were in the right lower lobe, three in the left lower lobe, and two in the left upper lobe. One of them was verified by bronchoscopy and one had had tuberculosis four years previously. In one patient metastases were found in the supraclavicular glands.

In nine patients metastatic tumours were met with in the lungs in addition to solitary tumours. All these patients had earlier undergone an operation for cancer. In two of these cases less than one month had elapsed between the operation on the primary tumour (hypernephroma in the right kidney and paraganglioma in the left suprarenal gland) and the pulmonary resection. In four cases (sarcoma in right thigh, adenocarcinoma of large intestine, fibrosarcoma of mammary gland, and carcinoma of large intestine) the corresponding period until pulmonary resection or the finding of metastasis varied from 2 to 2½ years. In three patients (malignant melanoma in gluteal region, osteogenic sarcoma and carcinoma of left suprarenal gland) the periods were 3 to 3½ years. Of these patients only one, with carcinoma of the suprarenal gland, in whom a segmental resection was done in both lungs, was alive fourteen months after the latest operation and still in good condition (Virkkula, 1959).

Of the benign tumours 41 (20.5 %) were granulomas. Bronchial carcinomas and granulomas together constitute 77 per cent of the total number. Tubercle bacilli had earlier been recovered from 25 of these patients, but were now found in only 11. All of these have been counted as tuberculomas.

Hamartomas are generally considered to be rare pulmonary tumours, but in fact they do not appear to be so (Davis *et al.*, 1956). In the Mayo Clinic series (Hood *et al.*, 1953) hamartomas were as numerous as bronchial carcinomas, numbering 16 per cent of all their solitary pulmonary tumours. They were the most common type of benign solitary lung tumour in our material, being found in 7 cases. They were as a rule round, of not more than 3 cm in diameter, and all were encountered in men. Two were situated in the right middle lobe, one in the right lower lobe, one in the left upper lobe, and three in the left lower lobe. Four of them were found by pure chance during X-ray examination.

A chronic inflammatory process seldom has the character of a distinct tu-

in different age groups, age and sex of individual cases, location of the tumour in the lungs, symptoms and their duration before treatment, diagnosis, operative procedures, complications and operative mortality, and to compare the findings with those of earlier authors.

CLINICAL MATERIAL

Our material comprises 200 cases of solitary lung tumour treated principally by pulmonary resection during the years 1948–1958. The cases were carefully collected on the basis of X-rays in accordance with the criteria employed by Davis *et al.* in 1956—with certain exceptions:

1. Tumours measuring more than 6 cm in diameter were included, especially if small when detected and of rapid growth. In 159 of the 200 cases the diameter of the tumour was 6 cm or less.

2. Tumours were considered solitary even if small satellite lesions were observed.

3. In the parenchyma the tumours were surrounded by aerated lung tissue. Cases were also included in which the pleura was involved only to a minor extent. On the other hand tumours which were distinctly evident in the hilus, mediastinum, diaphragm, or wall of the chest, were excluded.

4. The tumour must be round or ovoid in form. Lobulations must be minimal. The tumour was clearly delimited from the parenchyma, even if extreme sharpness of outline was not required.

5. There should be no calcium or cavitation within the tumour.

TABLE 1. Two hundred solitary pulmonary tumours.

Lesion	No. of cases	⩽6 cm diam.
Malignant:		
Bronchogenic carcinoma	114 (57 %)	81 (50.9 %)
Squamous carcinoma	49	
Undifferentiated carcinoma	35	
Adenocarcinoma	27	
Bronchiolar carcinoma	2	
Bronchial adenoma	3	3
Primary sarcoma	9	6
Lymphoma	2	2
Metastatic tumour	9	7
Total	137 (68.5 %)	99 (62.3 %)
Benign:		
Granuloma	41 (20.5 %)	41 (25.8 %)
Hamartoma	7	7
Chronic pneumonitis	4	3
Bronchogenic cyst	6	6
Post-infective cyst	2	1
Echinococcic cyst	1	—
Fibroma	1	1
Arteriovenous aneurysm	1	1
Total	63 (31.5 %)	60 (37.7 %)

6. Pneumonitis, atelectasis or regional lymphadenopathy should be completely minimal.

The number of cases with each type of lesion and the percentage of cases with tumours less than 6 cm in diameter are shown in Table 1.

Among our 200 patients, 90 of whom were operated upon by us, 137 (68.5 %) were malignant cases: 128 (64 %) were primary lung neoplasms and 9 metastases; 3 were bronchial adenomas of malignant character; there were 9 cases of primary sarcoma, 2 lymphomas and 114 (57 %) bronchogenic carcinomas, 49 squamous carcinomas, 35 undifferen-

age group, the youngest being 34 years old. Three of them had adenocarcinoma, one undifferentiated and one squamous carcinoma. There were two other malignant tumours in the same age group, making altogether seven malignant against eighteen benign tumours within that age group. Davis *et al.* also emphasize the importance of this observation, while others state that malignant solitary lung tumours are practically not at all encountered below 40 years of age. Our material likewise shows that malignant solitary lung tumours at the age of 30–39 years approach the ratio of one in three. The malignancy in the 40–49 and 50–59 age groups is substantially higher. The youngest cases of malignant tumour were three patients aged 15, 16 and 18, with metastatic lung tumours.

The distribution of the benign tumours by age groups was also studied. Granulomas are most equally distributed with the largest number, 13 cases, in the 20–29 age group. It is noteworthy that a large number of the 20–29 age group—13 out of 17 patients—had granulomas. The oldest patient operated upon for a benign tumour (bronchogenic cyst) was a 62-year-old woman.

The sex distribution presents a contrary picture. Only 51 patients (25.5 %) were women. Bronchogenic carcinoma occurred in 106 men and only in 8 women. The granuloma group contains 22 women and 19 men, metastatic tumours 5 women and 4 men, and chronic pneumonitis two of each sex. On the other hand the primary sarcomas occur more often in men than in women, seven men against two women. The hamartomas were all in men, whereas cysts were more frequent in women, seven women against two men. The two lymphoma cases were also women.

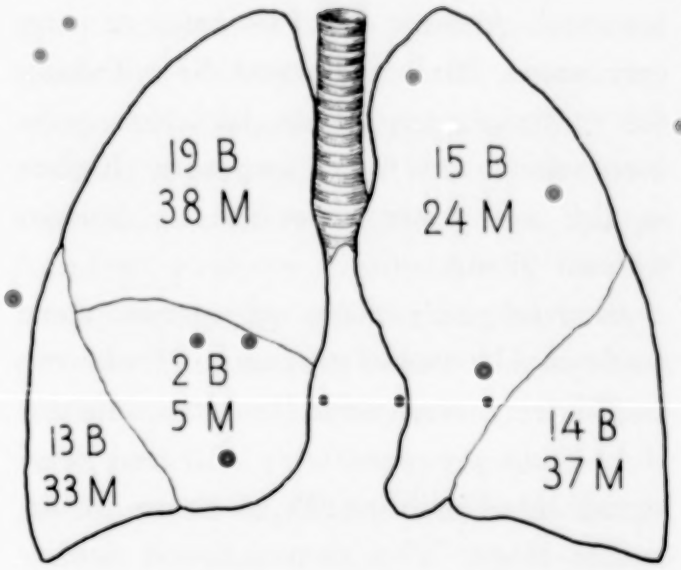


FIG. 1. The lobar distribution of solitary pulmonary tumours. Malignant (M), 137. Benign (B), 63.

The lobar distribution was almost equal (Fig. 1) with little difference between malignant and benign tumours. The location would not appear to affect the prognosis since all cases represented peripheral circumscribed tumours.

DIAGNOSIS

The preoperative diagnosis of solitary peripheral lung tumours is usually difficult. Their nature is not generally apparent until after thoracotomy. The anamnesis is seldom of help in making a preoperative diagnosis and, at times, may even be misleading. Nor are routine laboratory studies of any great diagnostic value. Many authors have regarded an elevated sedimentation rate in these patients as of no significance; others have thought it of serious import (Hood *et al.*, 1953); a third group finds no clear difference in sedimentation rates between patients with benign and malignant

TABLE 2. Age and sex distribution of 200 solitary pulmonary tumours.

Lesion	Total cases	Men	Women	Age, years 10–19	20–29	30–39	40–49	50–59	60–69
Malignant:									
Bronchogenic carcinoma	114	106	8	—	—	5	31	57	21
Bronchial adenoma	3	1	2	—	—	2	1	—	—
Primary sarcoma	9	7	2	—	2	—	3	3	1
Lymphoma	2	—	2	—	—	—	2	—	—
Metastatic tumour	9	4	5	3	—	—	2	3	1
Total	137	118	19	3	2	7	39	63	23
Benign:									
Granuloma	41	19	22	3	13	10	11	4	—
Hamartoma	7	7	—	—	1	1	3	2	—
Chronic pneumonitis	4	2	2	—	—	2	2	—	—
Bronchogenic cyst	6	1	5	1	—	2	1	1	1
Post-infective cyst	2	—	2	—	1	—	—	1	—
Echinococcic cyst	1	1	—	—	—	1	—	—	—
Fibroma	1	—	1	—	—	1	—	—	—
Arteriovenous aneurysm	1	1	—	—	—	1	—	—	—
Total	63	31	32	4	15	18	17	8	1

mour shadow. Four chronic pneumonites were classed as benign tumours since, despite thorough examination, their indolent character could not be established. These patients were aged 32–43 years, two being women and two men. Their symptoms were pain in the chest in two cases and hemoptysis in two others. Tumour cell, bronchoscopic and bacterial examinations were negative, as also were the histological studies following resection.

Bronchogenic cysts which lack connection with the bronchi may fill with secretion and assume the form of a solitary lung tumour (Tala, 1957). Six cases of such bronchogenic cysts occurred, three in the right lower lobe, one in the left upper lobe, and two in the left lower lobe. One case had an anomalous vein of pencil thickness direct from the aorta (sequestration). Five of these patients were female and one male. Two patients had postinfectious cysts, one in the left and the other in the right upper lobe; and one man had an echinococcic cyst in the right lower lobe.

Rarer forms of benign lung tumours were represented in our material by a 5×4 cm fibroma in the right upper lobe of a 30-year-old woman and by a 3×3 cm arteriovenous aneurysm in the right lower lobe of a 31-year-old man who suffered from vertigo. The former recovered after enucleation, the latter after lobectomy.

The age and sex distribution in our material is given in Table 2. The youngest patient was aged 15 years, the eldest 65. The patients suffering from bronchogenic lung tumours were rather older than the remainder. Bronchogenic carcinoma occurred in 106 men and only in 8 women. Of the latter, five were in the 30–39

present material did not include tumours with evident calcification, three cases did show calcific flecks in the tumour on closer examination. Two of these were tuberculomas and one a chronic pneumonitis.

Cavitation. Tumours which were cavitary when first detected were completely excluded from this study.

SYMPTOMS

In the group of bronchogenic lung carcinomas the tumour was discovered one to seven years before surgical treatment in 31 cases. In 19 cases 1 year had elapsed from the onset of symptoms or detection of the tumour, in 6 cases 2 years, in 4 cases 3 years, in 1 case 5 years, and in 1 case 7 years. The distribution of symptoms by types of lesion is shown in Table 3.

Most of our patients manifested no symptom, but the tumour was discovered by pure chance from a compulsory or voluntary X-ray. In some cases the symptoms became apparent after the patients were told that the X-ray had revealed a shadow on the lungs. Symptom-free patients numbered 52 in the malignant group and 34 in the benign group. The most common symptoms were cough and fever, which occurred in 33 patients in the latter group. Hemoptysis was an important diagnostic symptom. It was found that, of the 41 of our patients with hemoptysis, 30 had bronchogenic carcinoma, 2 bronchial adenoma and 1 metastatic tumour, while hemotysis occurred only in 8 cases of benign tumours. Five of the latter were granulomas, 2 chronic pneumonitis and 1 post-infectious cyst.

A symptom which may appear in a dramatic form is arthralgia. It is well known that this symptom may be associated with bronchogenic carcinoma, and still more often with peripheral

TABLE 3. Symptoms associated with 200 solitary pulmonary tumours.

Lesion	Total cases	Asymptomatic	Cough, Fever	Hemoptysis	Chest pain	Arthritis	Abdomial pain
Malignant:							
Bronchogenic carcinoma	114	40	29	30	10	3	2
Bronchial adenoma	3	1	—	2	—	—	—
Primary sarcoma	9	3	3	—	1	—	—
Lymphoma	2	2	—	—	—	—	—
Metastatic tumour	9	6	1	1	1	—	—
Total	137	52	33	33	12	3	2
Benign:							
Granuloma	41	23	11	5	2	—	—
Hamartoma	7	5	—	—	2	—	—
Chronic pneumonitis	4	—	1	2	1	—	—
Bronchogenic cyst	6	3	1	—	2	—	—
Post-infective cyst	2	—	—	1	1	—	—
Echinococcic cyst	1	1	—	—	—	—	—
Fibroma	1	0	—	—	—	—	—
Arterivenous aneurysm	1	1	—	—	—	—	—
Total	63	34	13	8	8	—	—

tumours. Among our 114 cases of lung carcinoma 28 had normal SR. Taking the material as a whole, however, sedimentation rates were generally higher in the malignant than in the benign tumour group.

Bacteriological studies of sputum were made in 41 cases of granuloma; tubercle bacilli were recovered from the sputum of 11 cases preoperatively and had been found in altogether 25 of them at an earlier stage. The simultaneous occurrence of tuberculosis and pulmonary carcinoma has been reported in a previous publication (Laustela *et al.*, 1955) and in one of our cases tuberculosis was simultaneous with bronchial adenoma (Laustela, in press). Such findings may delay treatment. A further possibility is the recovery of acid-fast bacilli from sputum, which is erroneously taken as a positive finding. In such circumstances it would appear that bacteriological tests of sputum should not be ascribed undue diagnostic importance. Similar conclusions were made by Waterman in 1948 and by Davis *et al.* in 1954.

The value of *cytological examination of sputum* has been stressed in the preoperative treatment of patients with solitary lung tumour (Hood *et al.*, 1953; Ford *et al.*, 1956; Wilkins, 1955). In the present material malignant cells were found in the sputum of 16 patients with peripheral circumscribed bronchogenic carcinoma (14 %).

Bronchoscopy may sometimes help in the diagnosis of these tumours, especially if the tumour is in the proximity of the hilus. A positive histological verification was obtained in 20 cases of bronchogenic carcinoma out of 114 (17.5 %).

Radiography. Since the tumour can be recognized radiographically, it is logical that the most elaborate attempts at diagnosis should be along radiological lines. The *size* of the tumour is no guide to its etiology or biological activity. In our material, for example, one bronchogenic carcinoma was 1.5 × 1.5 cm when originally detected, and another was 2.5 × 2.5 cm. In fifteen cases the diameter was 3 cm or less, while fifty-one ranged from 3 to 5 cm. The diameter of thirteen bronchogenic lung carcinomas was 5 to 6 cm, but there were only five granulomas of diameter 5–6 cm. All other tumours were smaller.

Sharpness of margin. In most cases it is impossible to distinguish malignant from benign tumours on the basis of size and margination. Nor was any clear difference observable in the present material, even if the contours of the benign tumours were perhaps more definitely marked.

Growth. A growing solitary lung tumour gives reason to regard it as malignant, especially if the growth is rapid. In thirty-one of the patients with bronchogenic lung carcinoma the period between the onset of symptoms or detection of the tumour and the start of treatment varied from 1 to 7 years. Davis *et al.* (1956) have also drawn attention to the varying size and growth of benign and malignant tumours.

Calcification. Several references are made in the literature to the fact that solitary lung tumours containing radiographically demonstrable calcium are benign (e.g. Fink, 1951; Abeles *et al.*, 1951; Culver *et al.*, 1950; Good *et al.*, 1951; Good *et al.*, 1953; Hodgson *et al.*, 1953; Davis *et al.*, 1956). Although the

pneumectomy. Another patient with primary sarcoma died in hospital without being operated upon. This patient had metastases in the supraclavicular node, and autopsy showed metastases in different parts of the body. The pathological diagnosis in all the aforementioned cases was bronchogenic carcinoma (2 squamous carcinoma, 2 adenocarcinoma and 3 undefined carcinoma). Two of our patients died of thrombosis, four with symptoms of cardiac insufficiency, and one of apoplexy.

Among postoperative complications there were two cases of pleural empyema. These responded well to aspiration and antibiotics. Empyema also occurred in one patient nine months after discharge, but here again the treatment was successful. On one patient with bronchogenic carcinoma postoperative hemorrhage necessitated a repeat thoracotomy, one patient developed thrombosis and one mild wound infection.

SUMMARY

The study covers 200 solitary pulmonary tumours treated at the Clinic of Thoracic Surgery of the Helsinki University Hospital during the years 1948 to 1958. Malignant types of tumour numbered 137 (68.5 %), among which 114 (57 %) bronchial carcinomas. The 63 (31.5 %) benign tumours included 41 (20.5 %) granulomas.

The main interest centred around the bronchial carcinomas and granulomas. These two groups together accounted for 155 cases, or 77 % of the total number of solitary lung tumours. The malignant group included 114 cases of bronchogenic carcinoma, 3 bronchial adenoma, 9 primary sarcoma, 2 lymphoma, and 9 metastatic tumours. In the benign group there were 41 granulomas, 7 hamartomas, 4 chronic pneumonites, 6 bronchogenic and 2 postinfectious cysts, 1 echinococcic cyst, 1 fibroma, and 1 arteriovenous aneurysm. The incidence of the malignant tumours in different age groups was studied. They were found even in young patients. Only 51 (25.5 %) of the entire series were women. The lobal distribution was even, without difference between malignant and benign types. Although most patients were asymptomatic, symptoms such as cough and fever, hemoptysis, chest pain, arthralgia and abdominal pain were noted especially in the carcinoma cases.

It is impossible to distinguish with certainty between the malignant and benign tumours except by thoracotomy. Cytological examination of sputum admittedly led to the detection of malignant cells in 14 % of the cases, and positive results were obtained with bronchoscopy (17.5 %). Other investigations lacked any diagnostic significance.

The mortality rate has been nil in cases when the tumour was removed by limited resection (52 cases). There were eight deaths (4 %) after lobectomy and pneumectomy (144 cases). One patient died of metastasis without operation.

This study fully confirms the opinion advanced in the literature that it is safest to perform thoracotomy on any patient in whom the X-ray reveals a solitary non-calcified shadow.

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tumours (Semple *et al.*, 1955), especially if the pleura is involved (Weirman *et al.*, 1954). Arthralgia was the first symptom in three of our patients, and all three were found to have bronchogenic carcinoma. Arthralgia in association with bronchogenic carcinoma appears to have a generally unfavourable prognosis (Davis *et al.*, 1956).

Other symptoms seem to be less common. Abdominal pain was the initial symptom in two of our patients, both of whom had solitary lung carcinoma.

TREATMENT

Our material, consisting of 200 solitary lung tumours, was treated surgically with the exception of one case. The types of operation for different types of tumour are shown in Table 4.

All operations were followed by a histological examination. Pneumectomy was done on altogether 71 patients, of whom 60 with bronchogenic lung carcinomas; lobectomy on 73 patients, 45 with bronchogenic carcinoma; segmental resection on 27 patients, 1 with bronchogenic carcinoma; enucleation on 22, comprising 4 carcinoma, 1 bronchial adenoma, 2 primary sarcoma, 1 malignant lymphogranulomatosis and 1 metastatic tumour; exploration on 1 bronchogenic carcinoma and 1 primary sarcoma; lung biopsy on 1 primary sarcoma; and supraclavicular node biopsy on 2 bronchogenic carcinoma and 1 primary sarcoma when metastases were found in the nodes.

The mortality rate with thoracotomy plus a limited resection (52 cases) has been nil. But after lobectomy and pneumectomy (144 cases) there were 7 deaths (4%), 4 after lobectomy and 3 after

TABLE 4. Operations and operative mortality: 200 solitary pulmonary tumours.

Lesion	Total cases	Pneumonectomy	Lobectomy	Segmental resection	Enucleation	Exploration	Lung or scalene node biopsy	Deaths
Malignant:								
Bronchogenic carcinoma	114	60	45	1	4	1	3	7
Bronchial adenoma	3	1	1	—	1	—	—	—
Primary sarcoma	9	3	2	—	2	1	1	1
Lymphoma	2	1	—	—	1	—	—	—
Metastatic tumour	9[a]	2	3	2	1	—	—	—
Benign:								
Granuloma	41	1	14	20	6	—	—	—
Hamartoma	7	1	1	1	4	—	—	—
Chronic pneumonitis	4	1	3	—	—	—	—	—
Bronchogenic cyst	6	—	3	2	1	—	—	—
Post-infective cyst	—	—	—	1	1	—	—	—
Echinococcic cyst	2	1	—	—	—	—	—	—
Fibroma	1	—	—	—	1	—	—	—
Arteriovenous aneurysm	1	—	1	—	—	—	—	—
Total	200	71	73	27	22	2	4	8 (4%)

[a] One not operated.

ACTA CHIRURGICA SCANDINAVICA, SUPPL. 245: 129–141, 1959

From St. Görans Sjukhus, Stockholm, Sweden

One Hundred Cases of Pulmonary Carcinoma, Analyzed with Reference to Tuberculosis

ALF WESTERGREN

With very few exceptions authors of articles and books dealing with pulmonary carcinoma have not considered the co-existence of malignancy and pulmonary tuberculosis. On closely examining the literature it is seen that the thought of such association received attention already in the middle of the last century and later in several publications, particularly during the last ten years. It was early maintained that the cancer process might originate from the pathologically changed tissue due to the tuberculous process.

The present author in 1954 presented eight cases of primary pulmonary carcinoma which might have originated on the basis of a tuberculous process, and in 1957 published a summary of the pertinent results on the same material now being reported upon. This material consists in all of the patients with primary pulmonary carcinoma admitted to the author's wards at St. Göran Hospital during the years 1944 to 1956. The total admission was approx. 2000 adult males and 4500 adult females among whom there were 69 male and 31 female cases of primary pulmonary carcinoma (incidence of 1.5 %). The surprisingly large percentage of female cancer cases, 31 %, might be attributed to certain factors in the composition of the material. The incidence of malignancy was 0.9 % for females, 3.5 % for males and 7.5 % for males over 40 years of age.

The cases are divided into four groups and are presented in two tables. Table 1 contains group III which consists of 34 cases of definite pulmonary tuberculosis with the carcinoma having developed within or in the immediate vicinity of the tuberculous process. Table 2 consists of groups II, I and 0 (cf. table headings). The 0 group cases gave no history or clinical finding indicating tuberculosis (though most of the cases were tuberculin positive). The average age for the males was 56 and for females 52. No appreciable difference could be shown in the distribution or average ages of the female cases within the four groups.

The histological diagnoses were performed in 87 cases and are designated in the tables as "Sq" = squamous cell carcinoma, "Oa" = oat cell carcinoma,

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TABLE 2.

Case No.	Sex	Age	Tob.	Cancer histol.	Tub. clin. rad.	Tub. post mort.
Group II. Chronic tubercul. proc. without local connect.						
35	m	51	+ +	Sq	+ +	0
36	m	45	+	Oa	+ + +	—
37	f	54	?	Sq	(+ +)	—
38	m	56	?	—	+ +	+
39	m	63	+	Sq	+ +	+
40	m	53	+ + +	Sq	+ + +	—
41	m	48	+ +	Sq	+ +	0
42	f	56	+ +	Ad	+ +	—
43	m	53	?	—	(+ +)	(+)
44	f	32	?	Ad	+ +	—
45	f	54	+ + +	Ad	+ +	—
46	f	57	+	Sq	+ +	—
47	m	58	+ +	—	+ + +	—
48	m	61	+	Sq	+ +	—
49	f	42	?	—	+ +	—
50	f	45	+ +	Ad	(+ +)	—
51	m	48	?	—	+ +	—
52	m	53	?	Sq	(+ + +)	0
53	m	44	+ + +	Sq	+ +	—
54	m	65	+ + +	Oa	+ +	(+)
Group I. Minimal, old t.b. No connection stated						
55	m	57	?	Sq	+ +	0
56	f	71	?	Oa	+	0
57	f	41	+ + +	Oa	+	—
58	m	55	?	Sq	+	—
59	m	47	?	Sq	(+ +)	0
60	m	62	+ +	Oa	+	+ +
61	m	57	?	—	+	—
62	f	57	?	Sq	(+ +)	—
63	m	50	+ + +	Ad	+ +	—
64	m	49	+ +	Ad	+	0
65	m	54	?	Oa	+	0
66	m	58	+ + +	Ad	+	—
67	m	59	+ + +	Sq	+	—
Group I. (cont.)						
68	m	51	+ +	Sq	+	—
69	m	43	?	Oa	+	—
70	f	66	0	Ad	+	—
71	m	42	+ + +	Sq	+	0
72	m	53	+ + +	Sq	+	+
73	f	38	0	Ad	+	0
74	m	66	+ + +	Sq	+	0
75	m	59	+	Sq	+	—
76	m	70	+ + +	Sq	+	—
77	m	50	+ + +	Sq	+	—
78	m	52	+ + +	Sq	0	+
Group 0. No t.b. proc. observed						
79	f	58	?	Ad	—	—
80	m	56	+ +	Sq	—	—
81	f	68	?	Sq	—	—
82	f	56	?	Oa	—	—
83	f	62	0	Oa	—	—
84	m	60	+ + +	Oa	—	—
85	m	47	+ +	Sq	—	—
86	f	33	0	Ad	—	—
87	f	58	?	Sq	—	—
88	f	49	?	Ad	—	—
89	f	40	+ +	Oa	—	—
90	f	51	+	Oa	—	—
91	m	63	+ + +	Sq	—	—
92	m	44	?	—	—	—
93	m	60	+ +	Sq	—	—
94	m	57	+ +	Sq	—	—
95	m	66	?	—	—	—
96	f	57	?	—	—	—
97	m	42	+ +	Sq	—	—
98	m	48	?	—	—	—
99	m	78	+ +	Sq	—	—
100	m	51	0	—	—	—

appears to be a histological difference. From the data available (58 cases) it has been found that 44 patients were heavy or "moderate" smokers (particularly in regard to cigarettes). Among these patients the distribution within the three histological types mentioned was Sq: 61.4 %, Oa: 20.5 % and Ad: 18.2 % respectively, as compared to 35.4 %, 28.6 % and 35.7 % respectively for the 14 cases who smoked insignificantly or not at all (cf. ref. 14).

In column 6 of the tables the clinical, particularly the radiological, findings of tuberculosis processes are recorded. Parentheses indicate that the diagnosis of tuberculosis was made in the past with no record of the intervening period (possibly negative finding). In column 7 (Table 1) the parentheses indicate that

TABLE 1. (group III). Fully pronounced pulmonary tuberculosis, locally connected to carcinoma.

(Case numbers in bold type are cases illustrated in the text.)

Case No.	Sex	Age	Tobacco	Cancer histol.	Tuberc. clinic. radiol.	TB	Tuberc. post mort.
1	m	66	+ + +	Sq	(+ + +)	(+ +)	—
2	m	56	?	Ad	+ + +	(+)	+ +
3	m	49	0	Ad	+ + +	0	+ + +
4	m	48	?	Sq	+ + +	(+ +)	+ +
5	m	69	+	Sq	+ + +	+ + +	+ + +
6	m	67	+ +	Sq	+ + +	?	+ +
7	m	58	+ + +	Sq	+ + +	+ + +	+ + +
8	m	57	+	—	+ + +	(+ +)	—
9	m	55	?	Sq	+ + +	(+ +)	+ + +
10	f	59	?	Oa	(+ + +)	(+ +)	+ +
11	m	45	?	Ad	+ + +	+ + +	+ +
12	f	50	?	Sq	+ + +	+ +	+ + +
13	f	37	+ +	Oa	+ + +	?	0
14	f	51	?	Ad	+ + +	+	0
15	m	64	+	Oa	+ + +	+ +	+ +
16	m	57	+ +	Sq	+ + +	+ + +	+ + +
17	m	55	+ +	Oa	+ + +	+ + +	+ + +
18	m	65	?	Sq	+ +	+ + +	+ + +
19	m	36	+ + +	Ad	+ +	?	+ +
20	m	71	?	Oa	+ +	+ +	+ + +
21	m	59	+ + +	Ad	+ +	+ +	0
22	f	44	?	Ad	+ +	0	—
23	f	46	?	Sq	+ +	(+ +)	+ +
24	m	41	?	—	+ +	0	+ +
25	m	63	+ +	Sq	+ +	0	—
26	f	51	+ +	Oa	+ +	0	—
27	m	71	+ +	Oa	+ +	+ +	+ + +
28	f	70	?	Oa	+ +	+ +	+ +
29	m	68	+ +	Sq	+ +	+ +	0
30	m	62	+ + +	Sq	+	+ +	—
31	m	41	+	Ad	+	+ +	0
32	m	53	?	Sq	(+ +)	0	+ + +
33	f	71	?	Oa	(0)	0	+ + +
34	m	68	+ +	Sq	(0)	0	+ +

and other undifferentiated forms, and "Ad" = adenocarcinoma and related types, including 3 or 4 cases with mixed forms (but none of semi-malignant type). From the cases with a histological diagnosis, the distribution and the male-female comparison were found to be as follows: "Sq" (52.9 % of the 87 cases) comprising 67.3 % of the male cases, but only 24.1 % of the females; "Oa" (24.1 %) consisting of 17.3 % of the males and 37.9 % of the females; "Ad" (22.9 %) comprising 15.5 % of the males and 37.9 % of the females. If the 47 clinical tuberculosis-positive cases (groups III and II) are compared with the remaining 40 cases in which tuberculosis was slight or not diagnosed, there was found practically the same distribution of the three histological types of malignancy. However, if the *smoking habits* of the cases are compared in this series, there

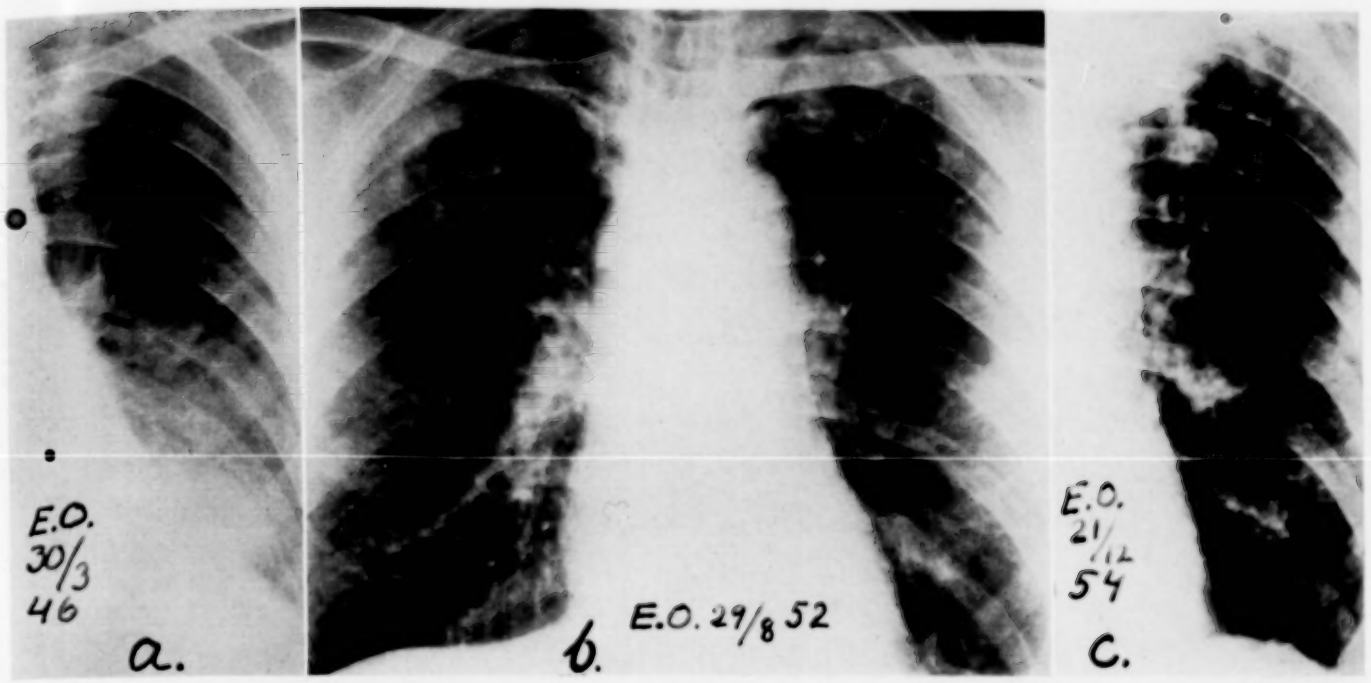


FIG. 2. Case 17 (m), b. 1899. Following an acute L. pleurisy, X-ray showed in 1946 (Fig. 11*a*), in addition to the pleural remainders, light central and apical chronic t.b. process. The films remained unchanged to and incl. 1950. However, in 1947 t.b.-spondylitis (L5–S1) was diagnosed, operated in 1948, subsequently healed. 1951 hemoptysis, now considerably increased processes with cavities bilaterally. Progress (Fig. 11*b*.) Thereafter a general regression (periodic chemotherapy treatment). From November 1954 impairment, with strong induration apically L. (Fig. 11*c*). TB steadily pos. 1951–1954. Died in January 1955 after an extensive hemoptysis. *Autopsy* showed large chronic t.b. cavity in apex of L. upper lobe, almost entirely filled by a tumour, originating from the upper wall of the cavity. The surrounding area showed chronic t.b. lesions. Apically to the R. similar t.b. processes (small cavity). No malignancy beyond the primary tumour (very low differentiation of indefinable type).

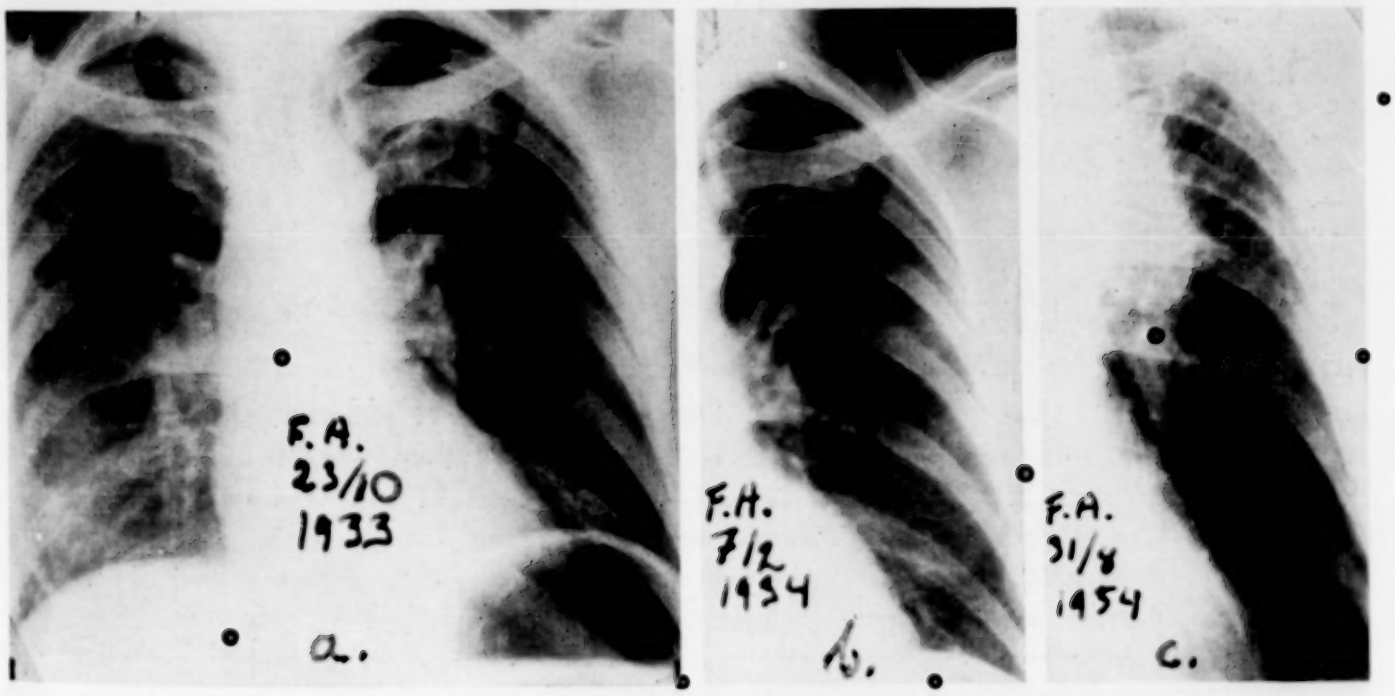


FIG. 3. Case 1 (m), b. 1888. In 1933, following hemoptysis, bilateral pulmonary tuberculosis was diagnosed. Varying spreading, particularly with a large cavity-formation in the L. apex (Fig. 1*a*). Very good regression (Fig. 1*b*). Coughing in 1954 with the appearance of a large tumour shadow in approximately the same area as the cavity in 1933 (Fig. 1*c*). Histolog. squamous cell carcinoma.

bacilli were not registered during the two years prior to the diagnosis of malignancy. In practically all of the remaining cases the positive finding of bacilli has been confirmed by guinea pig tests and/or culture. The post mortem column contains only the findings pertaining to tuberculosis. "0" indicates lack of positive information in the records or that tuberculosis was directly stated not to be present.

In the following, twelve cases from group III are presented, showing more or less marked relation between tumor and t. b. cavity, as well as different types of active or healed tuberculosis. In the first two cases (Nos. 5 and 17 in Table 1 — Figs. 1 and 2) the origin of the carcinoma from a tuberculous cavity was clearly verified post mortem. In the following four cases (Figs. 3, 4, 5, 6) a similar pathogenesis seems quite acceptable and probably also as to the cases 14 and 15 (Figs. 7 and 8). The remaining four cases are chiefly brought to show the coincidence of active, progressive tuberculosis and carcinoma.

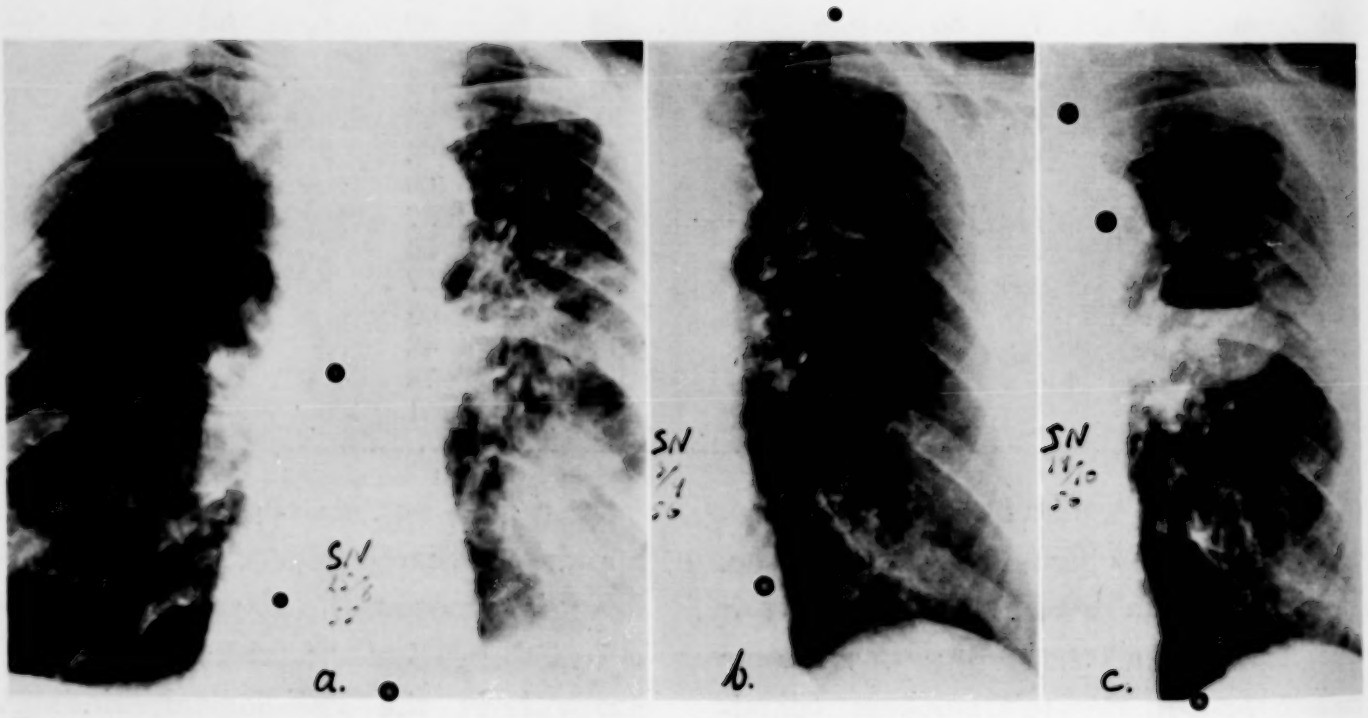


FIG. 1. Case 5 (m), b. 1885. Coughing since 1935. An X-ray in 1950 revealed chronic t.b. apically and perihilary, chiefly on the L. side. In 1955 coughing and fever; X-ray (Fig. 3*a*) now showed wide-spread acute progress in the L. lower lobe with some cavitation. TB pos. Good regression with chemotherapy (Fig. 3*b*), later on followed by deterioration with large cavitation (Fig. 3*c*). *Autopsy* in December revealed dispersed cancer (squamous, somewhat horny) in left lower lobe, emanating from the cavity in the wall of which some light t.b. changes could be noticed. Some healed t.b. in both apices.

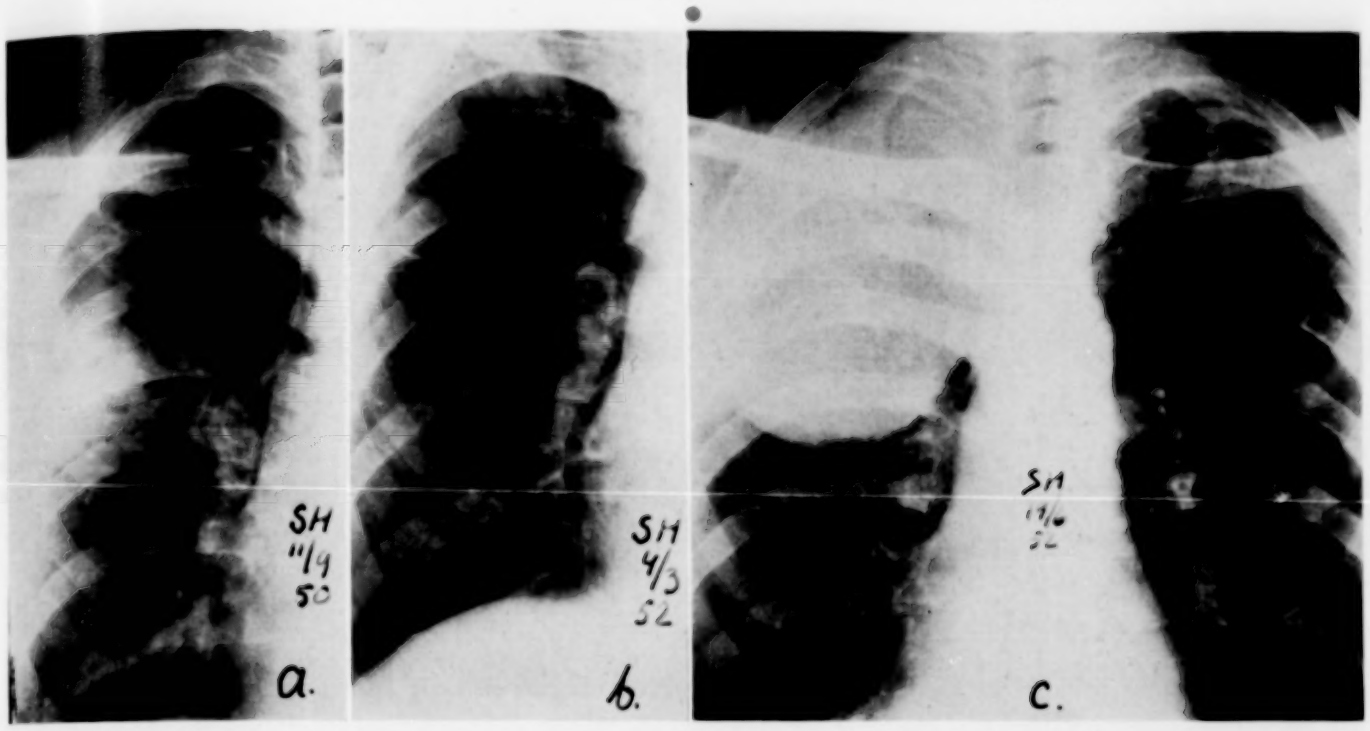


FIG. 6. Case 11 (m), b. 1909. Hemoptysis 1949. X-ray showed slight chronic apical changes and a slight density with some suspicion of cavity formation subapically-laterally on the R. side. Spontaneous relative regression. 1950 large hemoptysis and now (Fig. 6*a*) the process appeared much more clearly with two definite cavities. TB repeatedly pos. Practically full regression by chemotherapy, but in 1951 cavity again seen. Again good regression (Fig. 6*b*). 1952 operation (polystan plombage). Subsequently satisfactory X-ray and good condition in every respect (Fig. 6*c*) up to 1954, when multiple pains began. X-ray unchanged. *Autopsy* 1954 showed a localized tumour the size of a hen's egg (low differentiation, proximately adenocarcinoma emanating from the area of the right upper lobe bronchus (with metastases extrapulmonarily), and minimal, healed t.b.).

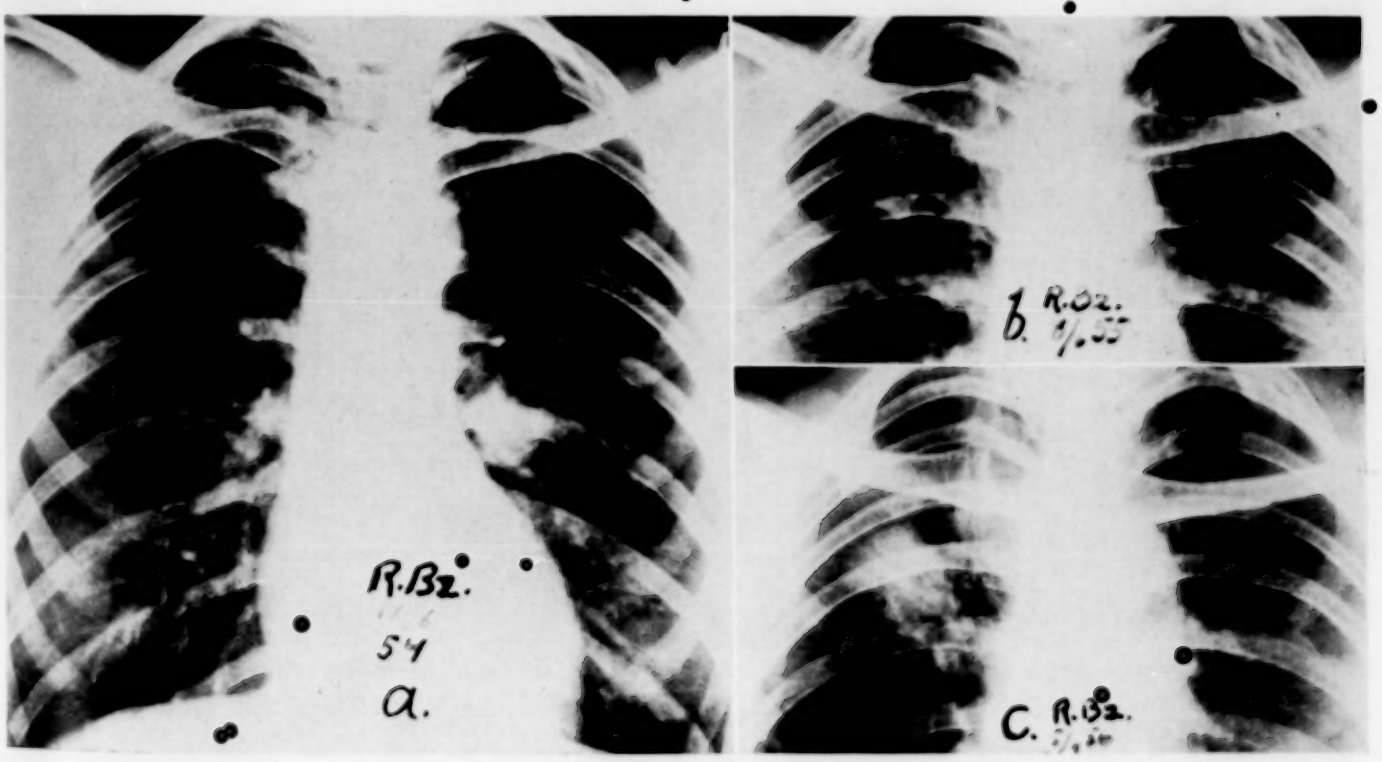


FIG. 7. Case 14 (f), b. 1905. Hemoptysis 1954. T.b. in the apex of the L. lower lobe (Fig. 8*a*). On some films a small, thin spot could also be traced subapically R. After chemotherapy resection of the L. lower lobe apex (histol. typical t.b.). 1955 carcinoma of the R. breast was diagnosed and immediately operated upon. Now a definite infiltration subapic. R. was seen. Progress (Fig. 8*c*). Segmental resection within the R. upper lobe. Well-restricted tumour, histol. proximately primary

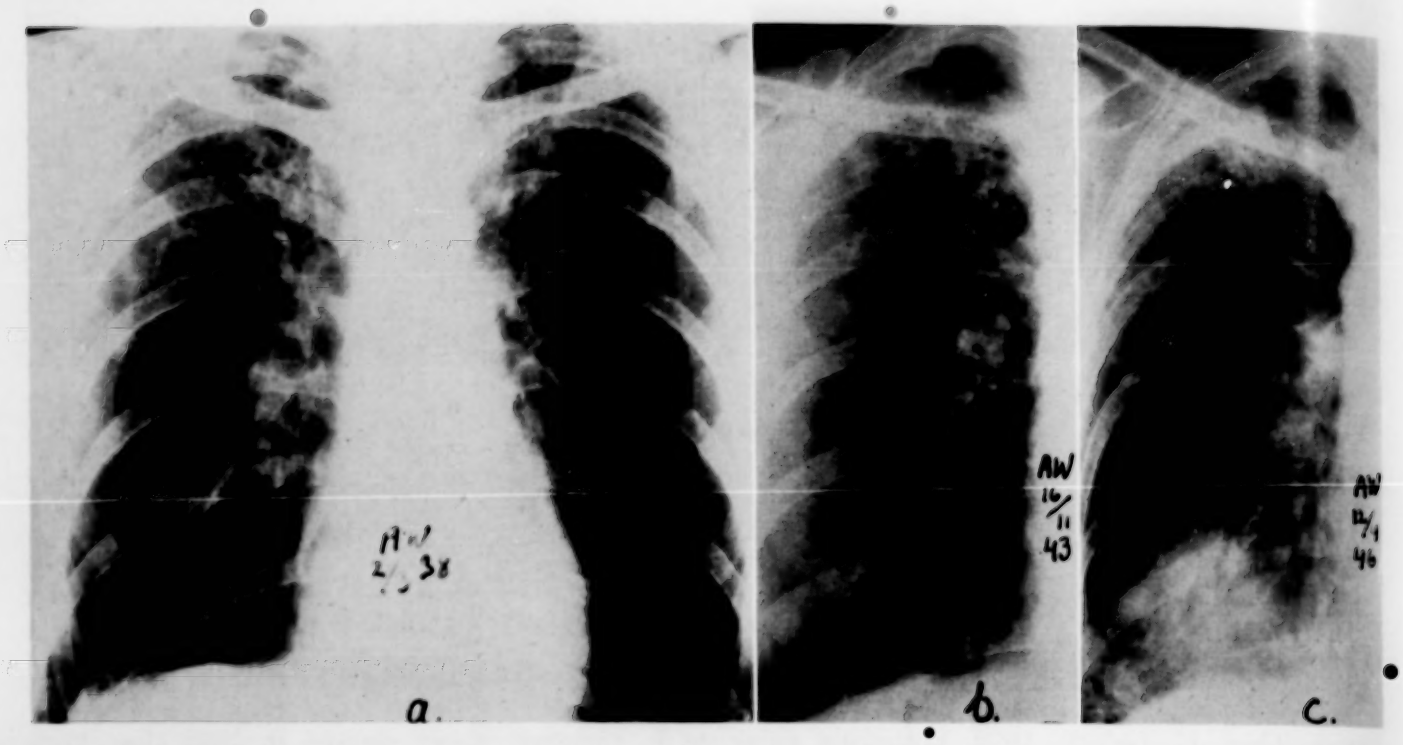


FIG. 4. Case 3 (m), b. 1897. In 1938 chronic bilateral apical t.b. was discovered, chiefly on the right side (Fig. 2*a*). In 1943 some progress with suspected cavity in the R. apex (Fig. 2*b*). From 1944 progress within the R. lower lobe increased (Fig. 2*c*). At *autopsy* in August 1946 bilateral fibrous t.b. was discovered perihilary and in the upper lobes, mostly on the R. side. The entire R. lower lobe was filled wth pneumonic growing cancer (histol. adenocarcinoma).

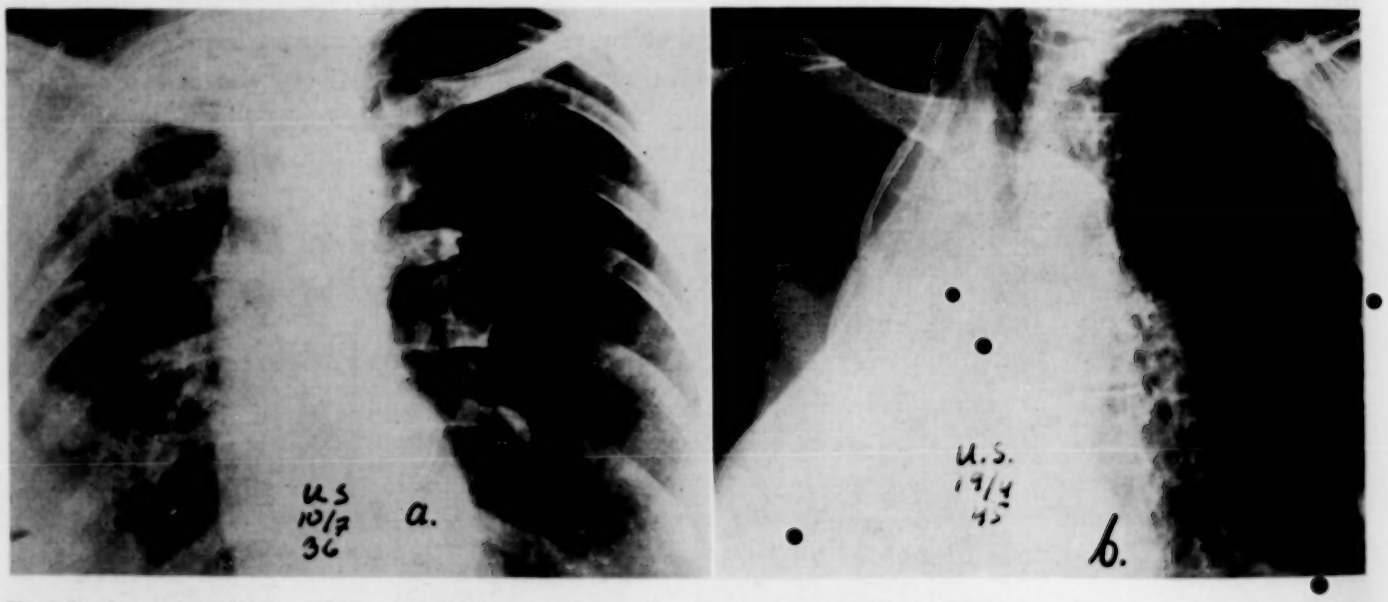


FIG. 5. Case 10 (f), b. 1889. 1934 dispersed R.-sided t.b. with cavity (Fig. 5*a*). TB pos. Thoracoplasty Subsequently, symptom-free and roentgenologically healed. (1941 positive finding of bacilli once but otherwise no signs of impairment.) 1948, pains and increased SR. X-ray unchanged 1936–41 (Fig. 5*b*). General impairment. X-ray picture still unchanged. *Autopsy* in June 1949 showed R. lung almost entirely invaded by cancer (oat cell carc.). Macroscopically no tuberculosis, but microscopically t.b. changes in small areas of R. lung.

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alveolar cell cancer: quite different from the breast carcinoma. After one year general impairment. *Autopsy* in February 1958 showed dispersed metastasis of the breast carcinoma, *inter alia* in the L. lung. Malignancy was also found in the R. hilar and adjacent area but here the cell type was the same as the primary pulmonary carcinoma. "No t.b.-process".

(In this connection it might be mentioned that the series contained another two cases, females, of multiple carcinoma of different histology.)

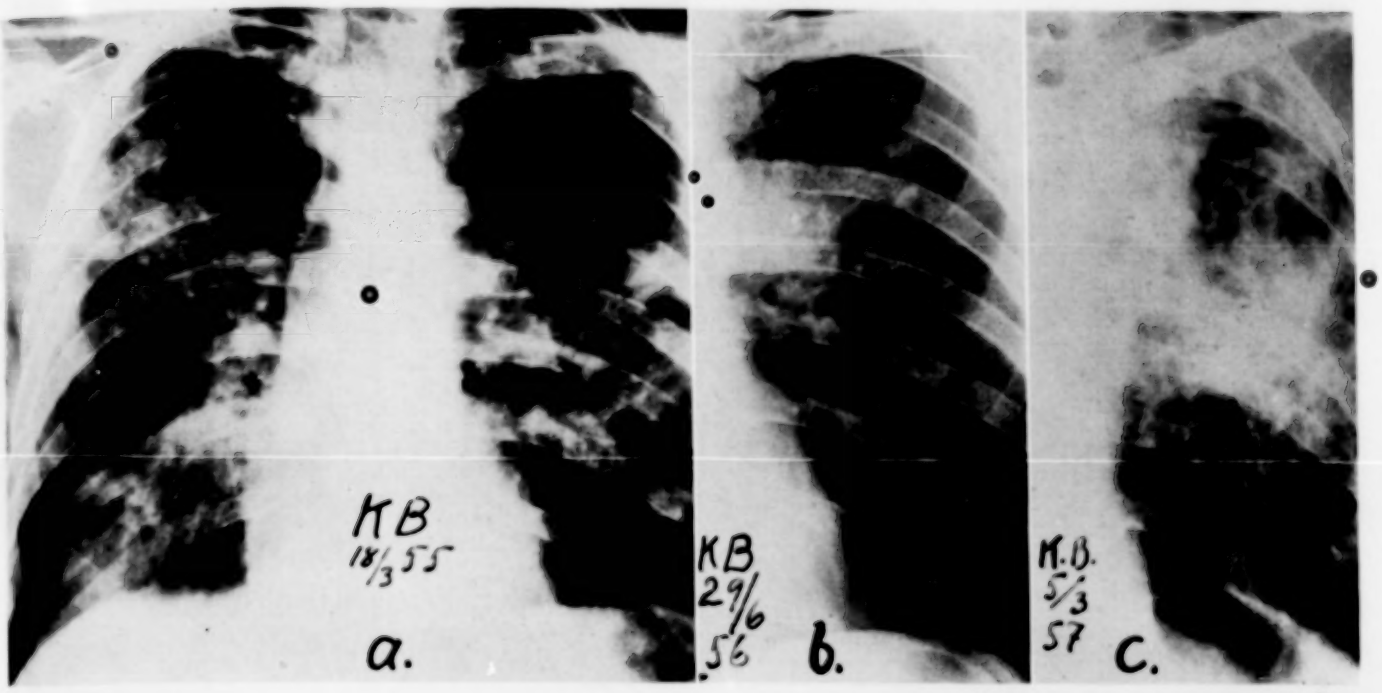


FIG. 10. Case 16 (m), b. 1898. 1955 (Fig. 10*a*) acute, highly dispersed, bilateral t.b. processes with cavities. TB pos. Almost full regression after chemotherapy but subsequently a central induration appeared on the left (Fig. 10*b*). Bronchograph. tumour around anterior branch of L. upper lobe bronch. Lobectomy. (Histol. moderately differentiated, somewhat horny, squamous cell cancer.) Good health for at least four months. In February 1957 an induration appeared apically within the remaining L. lower lobe, which quickly spread (Fig. 10*c*) and now lesions also appeared in the R. lung. TB pos. *Autopsy* in March showed t.b. processes of generally a highly acute type, mainly within the upper part of the L. lower lobe. No cancer.

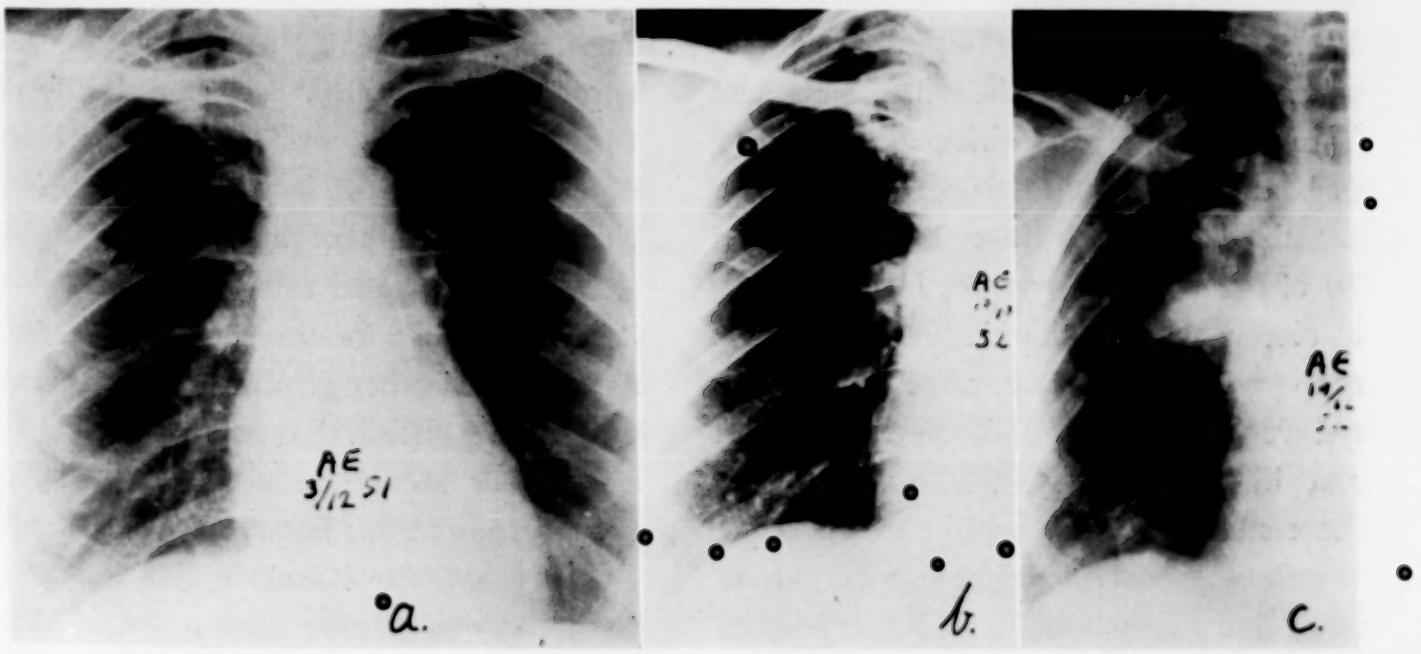


FIG. 11. Case 12 (f), b. 1902. 1949 minimal bilateral apical changes, mostly on the R. side, somewhat increased in 1951 (Fig. 7*a*). 1952 progress apically-medically R. with cavity-formation (Fig. 7*b*). TB pos. Rapid deterioration (Fig. 7*c*). *Autopsy* in February 1953 showed cavernous t.b. in the R. upper lobe (with atelectases of t.b. origin) together with polymorphous squamous cell carcinoma.

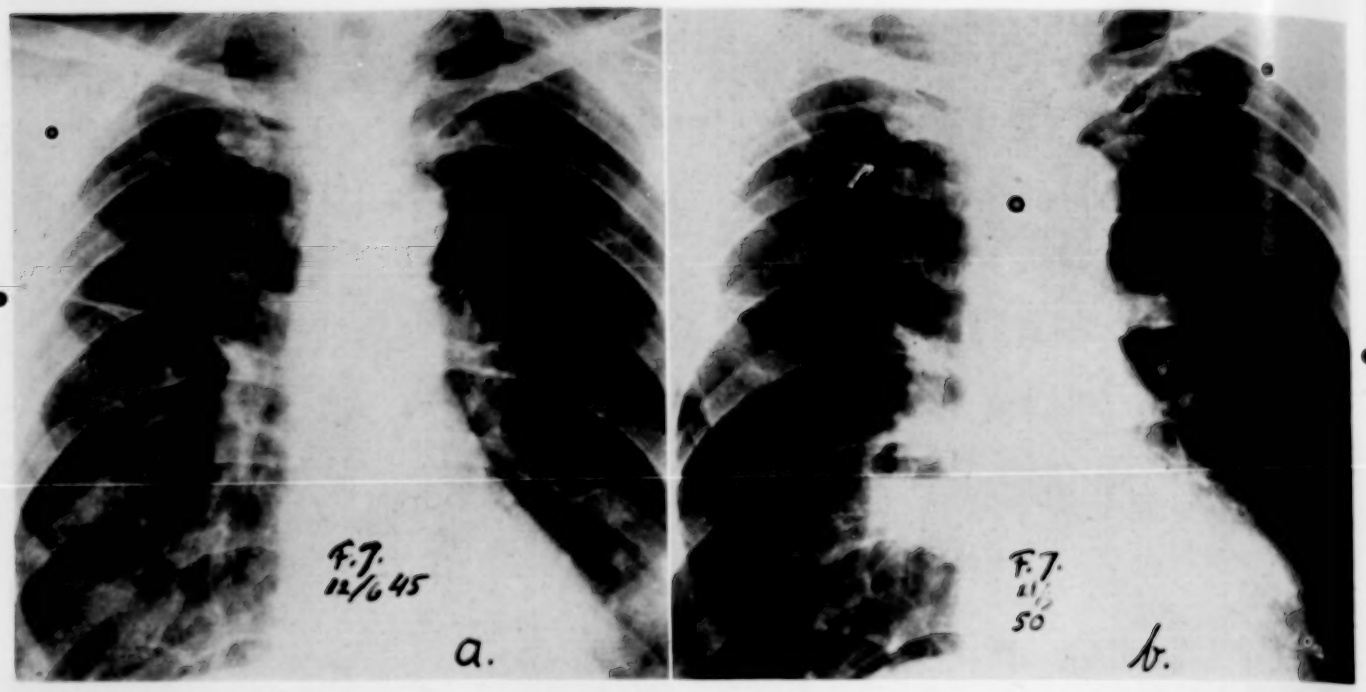


FIG. 8. Case 15 (m), b. 1886. On X-ray 1945, a somewhat indurated R. hilus with an interlobar bride and minimal disseminated spots bilaterally (Fig. 9*a*). Unchanged to and incl. 1949. Slight hemoptysis 1950. Cavity centrally R. (Fig. 9*b*). Bronchoscopically scarious constriction of the R. upper bronchus together with some indefinable acute swelling (middle and lower lobe bronchis normal). TB pos. Continued progress. *Autopsy* in January 1951 showed dispersed, highly gangrenous cancer (oat-cell) in R. lower lobe with destruction of the lower lobe bronchus. Indurated t.b. lesions within the apical areas.

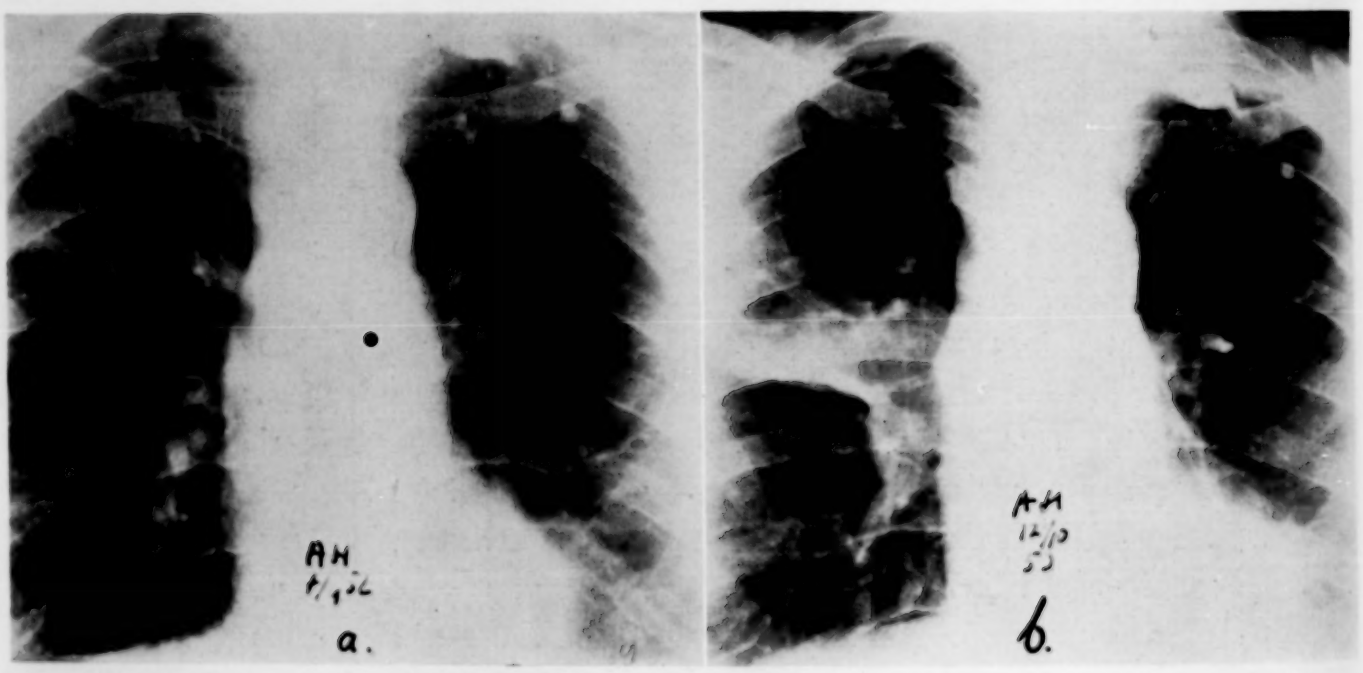


FIG. 9. Case 7 (m), b. 1895. Left pleurisy in 1916, hemopt. 1920. Slight apical t.b. bilat. After acute "cold" infection 1952 X-ray showed (Fig. 4*a*) increased apical process, some atelectasy R. TB pos. Bronchoscop. only some stenosis of indefinite origin within one branch of R.u.l. br. After chemotherapy good regression of the R. ap. density, but later marked advancement (Fig. 4*b*). Brsc. considerably increased, tumour-like stenosis. (Histol. squamous cell carc.) Pulmectomy. *Autopsy* in March 1953 reported greatly dispersed chronic t.b. within remaining left lung.

according to the pathological-anatomical diagnosis). In a Swedish investigation by Källqvist (13) the incidence of pulmonary malignancy detected was definitely less than the values presented here. This is partially explained by the fact that more cases of pulmonary disease of non-tubercular origin were admitted to St. Görans Hospital. However, in calculating the frequency of cancer-tuberculosis from Källqvist's tables, it will be found that among Källqvist's primary pulmonary cancer cases (28 or 34 cases) a combination existed with tuberculosis in 11 (12) cases. This corresponds to an incidence of 39.2 % or 35.3 %, and is in good agreement with the present author's figure of 34 %. Drymalsky & Sweany (7), found that in 57 autopsy cases of bronchogenic carcinoma 15 cases (26 %) had tuberculosis with bacilli being found sometime during their lifetime. Of these 15 cases, 8 showed pulmonary tuberculosis post mortem (five active and three latent lesions) and in not less than 7 tuberculosis findings at autopsy were reported as negative. Attinger (1) found among 758 post mortem examinations of presumable pulmonary tuberculosis 89 cases of cancer of the lung of which in 12 cases (14 %) there was conjunction with tuberculosis. In seven of these 12 cases the cancer had clearly originated in tuberculous tissue. Seyfarth (14), in a similar series of 323 cases, found 25 cases of pulmonary malignancy, of which seven cases (28 %) were associated with tuberculosis. In another series of 1103 autopsied pulmonary malignancy cases Seyfarth stated combination with tuberculosis in 11.4 %. Sprovieri *et al.* (20) analyzed 100 cases of pulmonary carcinoma and found a certain association with pulmonary tuberculosis in 17 % and a probable association in a further 32 %. Five papers from the 1930's and 1940's indicate t.b. incidences of 5–10 %, whereas in five more recent reports frequency figures for the combination of tuberculosis and pulmonary cancer of about 20 % are given.

Finke (8) has analyzed 159 post mortem cases of primary pulmonary carcinoma patho-anatomically as well as anamnesically. Chronic bronchial deseases were reported in at least one third of all the cases, but if only the cases with a detailed clinical history were regarded, three quarters presented chronic bronchial disease. Pulmonary tuberculosis had been diagnosed in 12 cases (7.5 %). Oudet and Roegel (17) have recently reported on 23 cases of bronchial malignancy together with tuberculosis, of which there was in 16 cases a close local relationship, while in another 3 cases a lesser intimacy was found. Only in four cases could no local relationship be detected. Murasawa & Altmann (15) have published a detailed paper on 570 autopsies with pulmonary disease. They reported 39 cases of primary pulmonary carcinoma of which 14 cases showed a close relationship between carcinoma and active tuberculosis, 10 cases showed pulmonary tuberculosis without local relationship, and in 15 cases "no tuberculosis" had been recorded (2 cases in the last group, however, had been bacilli-positive during their lifetime). The frequency in this series of close relationship was 35.9 % (compared to the present author's 34 %). The co-existence

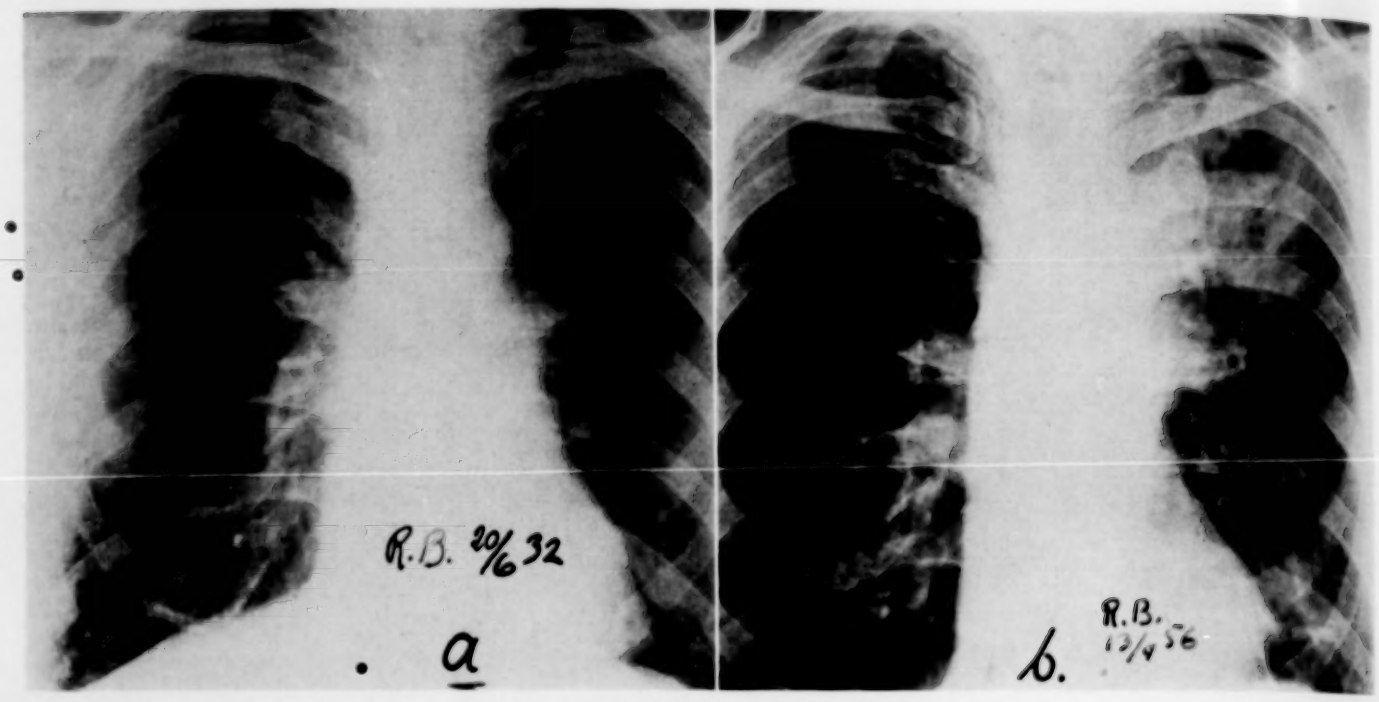


FIG. 12. Case 20 (m), b. 1885. 1932 light induration medially in L. apex with elevation of hilus (Fig. 12*a*, more clearly seen in 1951). 1956 acute fever and X-ray (Fig. 12*b*) now showed markedly active tuberculosis process in upper lobe. TB pos. *Autopsy* showed walnut size tumour in L. upper lobe bronchus (histol. typical oat cell carcinoma) and within upper lobe macro- and microscopically confluent t.b. processes, partly of acute type.

RESULTS AND DISCUSSION

In 54 of the 100 cases of pulmonary malignancy definite tuberculosis processes were diagnosed clinically and/or at autopsy, of which carcinoma in 34 cases had developed in the same area as the pulmonary tuberculosis, with 23 of these being recorded as positive as to finding of bacilli. Of the 23, 16 were positive for bacilli during the last 1–2 years. In 19 of the 28 autopsy cases in group III, a closer analysis had shown that the malignancy probably originated from tuberculous tissue. (A similar origin was likely in many, perhaps most, of the remaining cases within this group.) Within the 34 cases in group III, there were five cases with negative report at autopsy in respect of tuberculosis; however, the development of the tumour had been roentgenologically locally correlated to an evident tuberculous process (in four of these five cases the clinical finding of TB had been positive). In a few papers on this subject it has been pointed out that the carcinoma may, more or less entirely, destroy tuberculous tissue, and this phenomenon is probably most common in such cases where the tuberculosis has spread only slightly. (The possibility of the malignancy developing on the basis of a small process is hardly much less than in the case of more extensive lesions.) With regard to the cases in Table 2 it is, for the reason just mentioned, as well as on other grounds, by no means out of the question that more tuberculosis and closer local connection may have existed than it has been possible to find.

The majority of similar investigations from more extensive material originate from pathology-anatomy institutions, and in some papers the size and the composition of the entire clinical material is indicated (however, the cancer cases only seem to have been recorded

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of lung cancer and pulmonary tuberculosis was 61.5 %, which corresponds to the figure of 54 % of the present series. Murasawa & Altmann reported the histological diagnoses as Sq. in 53.8 %, Oa in 33.3 % and Ad in 12.8 % and were also unable to discover a cell type predilection to tuberculosis. They reject a genetic relationship between tuberculosis and cancer and consider the coexistence to be explainable from a purely statistical point of view.

The great majority of investigators in this field more or less definitely associate the etiology of cancer being favoured by the tuberculosis process. In addition to the above-mentioned papers only a few (3, 4, 10, 11, 21) may be mentioned from the many pathological-anatomical studies. Schwartz (18) as well as Woodruff (24), from different points of view, have shown that the origin of the cancer process can frequently be proved in older, often calcified pulmonary foci or tracheo-bronchial lymph-nodes. Investigations dealing with the general malignancy relationship to infectious processes etc. (e.g. 2, 5, 9, 12, 16, 23) may also be brought to mind.

Finally it may be mentioned that some authors in this field, like myself, have postulated that the increased frequency of pulmonary cancer might, to a certain extent, be explained by the simultaneously increased tuberculosis frequency among the older age group.

SUMMARY

Among 100 cases of primary pulmonary carcinoma, discovered within a chest clinic material, fully pronounced tuberculosis lesions with local relationship to the tumor were found in 34 cases (demonstrable intimate relationship in 29 cases). In 23 of the 34 cases tubercle bacili had been reported, of which in 16 at the time of the malignancy. More detailed presentation, including X-ray pictures, is given for 12 cases of different types. Twenty other cases showed pulmonary tuberculosis without any noticed local relationship to the carcinoma, and in another 24 cases only minimal tuberculous lesions were found.

Evident tuberculosis processes have thus been recorded clinically and/or patho-anatomically in 54 %, with local relationship in 34 % of the 100 cases. Incidences of approximately the same magnitude were obtained when analyzing some of the more extensive investigations of the last decade. On account of the literature and the present report it seems to be beyond doubt that local tissue abnormalities, particularly those of a tuberculous origin, constitute an important factor in the genesis of pulmonary carcinoma.

If it had been possible to make further analyses, more tuberculosis and a closer relationship would most probably have been demonstrable. Attention must be paid to the fact that negative post mortem findings pertaining to tuberculosis are by no means decisive as the tuberculous tissue is in many cases destroyed and more or less eliminated during the development of the carcinoma.

In 87 cases histological type and in 58 also relationship to smoking habits is reported. The frequency of squamous cell carcinoma among the smokers was 61.4 % and among non-smokers 35.4 %.

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long time after the injury occurred. Kirkpatrick (1950) performed pulmectomy immediately after the injury. Sanger (1945) succeeded in repairing, with good results, two cases of bronchial rupture due to gunshot injuries in World War II. Griffith (1949) reported the first successful treatment of a case of partial rupture of the bronchus with secondary stenosis, that was not due to penetrating trauma, by restoration of the bronchial continuity. Weisel and Jake (1953) reanastomosed a complete bronchial rupture. To date 37 cases of bronchial repair have been reported (Tyson, Watson & Sibley, 1958). Most of these were operated upon months or years after the injury. However, it is stressed (Sanger, 1945; Richards & Cohn, 1955; Sheehy & Hopeman, 1955; Samson, 1956) that repair should if possible be made immediately after the injury. In Scandinavian literature two cases operated upon by Crafoord have been reported by Norlin (1955) and one by Peräsalo (1956).

CLINICS

A bronchial rupture is mostly combined with other serious injuries. Massive bleeding, shock and multiple thoracic fractures then often dominate the clinical picture and the bronchial rupture is easily overlooked. The bronchial rupture presents two main findings, viz. pneumothorax and subcutaneous air emphysema. It is characteristic that a pneumothorax is persistent despite repeated aspirations (Paulson, 1951; Fowler, 1955; Ellis, Andersson & Hayles, 1955; Bücherl & Koch, 1957). In the cases where the rupture is located within the mediastinum a pronounced subcutaneous air emphysema is usually the most apparent sign. Bronchoscopy and bronchography, if the rupture possibility is kept in mind, make the diagnosis quite simple.

If the patient survives the acute injuries, the course of the case depends to a great extent on whether the bronchial rupture is *partial* or *total* (Tyson & Lyle, 1942; Holinger, Zoss & Johnston, 1948; Deloyers, Dumont, Duprez, Durieu, Dedercq & Rheinhold, 1949; Samson, 1955; Mahaffey, Creech, Boren & De Bakey, 1956; Liaras, 1956; Santy, Lagèze & Latarjet, 1957). *A partial rupture* results as a rule in a bronchial stenosis with secretory stagnation and secondary infection which usually, more or less, destroys the lung parenchyma. In cases where the rupture is *total* the lung will collapse. The bronchi become filled with a gluey secretion from the mucous glands (Santy, Berard, Bochet & Fraisse, 1945; Priest, 1950; Weisel & Jake, 1953; Dalgleish, Hazen & Kinnear, 1954; Suavage, 1954; Krauss, 1955), but infection does not, as a rule, develop and the pulmonary tissue is *not* destroyed (Holinger, Zoss & Johnston, 1948). A lung that has collapsed in this manner may after suction of the bronchi and repair of the bronchial rupture again expand and resume its normal ventilation even many years after the injury (Samson, 1956—fifteen years after the injury; Mahaffey, Creech, Boren & De Bakey, 1956—eleven years after the injury). The clinical difference in prognosis between partial and total bronchial rupture, agrees well with experimental investigations (Tannenberg & Pinner, 1942;

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Traumatic Bronchial Rupture

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One of the emergencies of greatest clinical importance found in severe trauma of the thorax is a rupture of the intrathoracic trachea or any of the main bronchi.

It is comparatively rare that such an emergence is diagnosed in vivo; it is usually a post-mortem finding, often with other serious injuries. Up to date between 70 and 80 cases have been reported (Krinitzki, 1928; Hasche, 1953; Mahaffey, Creech, Boren & De Bakey, 1956; Tyson, Watson & Sibley, 1958). With the increasing rate and severity of traffic accidents, this emergency will, most likely, occur more frequently in the future.

As a rule one of the main bronchi ruptures 1–2 cm distal to the carina. This is possibly due to the anatomy of the region, since the rupture usually occurs at the junction of the fixed and mobile parts of the respiratory tract.

As an analogical example may be mentioned a rupture of the aorta root and of the influx points of the venae cavae in the right heart in severe thoracic trauma.

The rupture of the bronchus is most commonly due to a sudden massive compression of the thorax, i.e. being run-over, compressed behind a steering wheel or some heavy object. Sometimes a fall from a considerable height may be the cause. A most likely explanation of the rupture is when there is simultaneously a closed glottis with suddenly increased intrathoracic pressure (Schönberg, 1912; Thompson & Eaton, 1955).

The first to report that a bronchial rupture was not necessarily incompatible with life was Krinitzki (1928). He found, on sectioning the lungs of a 31-year-old woman, that one lung was completely atelectatic due to the rupture of a main bronchus which was clinically undiagnosed for 20 years following an accident. Jones & Vinson (1939) were the first to establish the diagnosis clinically. With the possibility of establishing the diagnosis clinically, the problem of its therapy became a reality. At first different palliative methods were attempted, such as plugging off the involved bronchus (Clerf, 1940; Löffler & Nager, 1941) or pneumothorax (Tyson & Lyle, 1942), but later pulmectomy became the method of choise (Kinsella & Johnsrud, 1947; Holinger, Zoss & Johnston, 1948). As a rule, pulmectomy was performed a

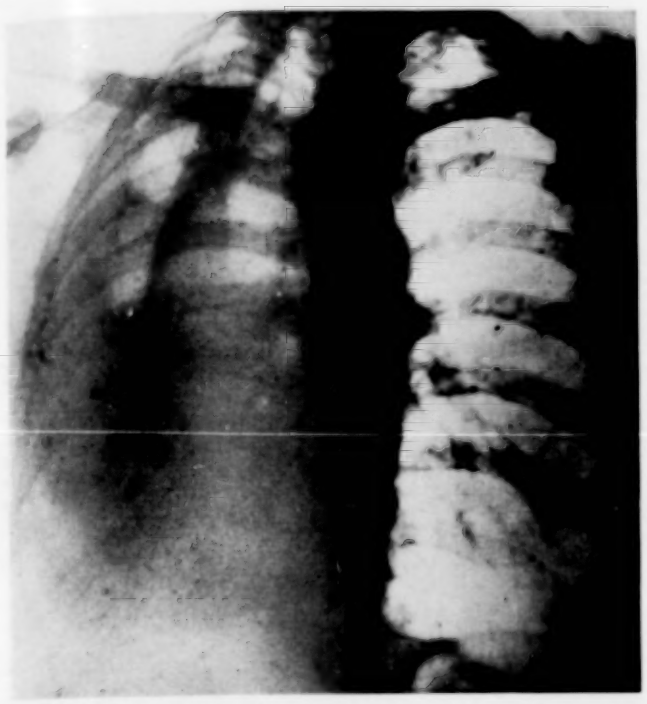


FIG. 1. Lung roentgenogram about 2 months after chest injury. Repeated attempts to arrest pneumonthorax without effect. Marked shifting of the mediastinum to the right.

On arrival there his general condition was somewhat poor and he had lost a great deal of weight. Even at rest he had moderate cyanosis of the lips. This was more marked with moderate physical effort, such as rising from a lying position. This was accompanied by marked dyspnoea. Chest X-ray showed a collapsed right lung with the mediastinum markedly pulled over to the right (Fig. 1).

Bronchography: The contrast media suddenly stopped 1 cm from the carina in the right main bronchus (see Fig. 2).

Bronchoscopy: At the level of the carina the right main bronchus was filled with a comparatively firm tissue which gave the impression of being an organized connecting tissue. Excision of it caused minimal bleeding and demonstrated a lumen which finally widened to the width of a knitting needle. The bronchus was not air-carrying, upon coughing there was no appearance of secretion. There was found, however, a shiny bloody mass coagulated under the organized connecting tissue (A. Thulin).

Spirometry (performed in a lying position owing to poor general condition): total lung capacity (TLC) was reduced to about half of the estimated normal value. The other partial volumes, vital capacity (VC), functional residual capacity (FRC), and residual volume (RV) were reduced in relative proportion. The effectiveness of the ventilation, judged from the wash-out of nitrogen gas during oxygen breathing, was practically normal. Lung clearance index without remark. Owing to the poor general condition of the patient, maximal breathing capacity (MBC), and maximal expiratory volume (MEV) were not determined (see table 1) (Svanberg).

19 September, 1956 (H. B. W.): *Thoracotomy + end-to-end anastomsis of the bronchial stumps*. The right lung was totally collapsed. The pleura cavity was filled with a slightly haemorrhagic exudate, partly liquid, partly gelatinous. The lung was freed and the lung hilus dissected. A complete tear of the right main bronchus was found just under the left azygos vein. The vein was divided and the ruptured broncheal stumps freed from the interposing fibrous tissue, due to organized blood. Fairly large amounts of a gelatinous clear material was suctioned from the bronchus of the collapsed lung. After complete suction of the material, pure oxygen was blown into the lung through a rubber tube placed in the bronchus and the lung re-expanded rather easily. The bronchial ends were trimmed and joined together by a row of isolated sutures with atraumatic catgut No. 000. The row of sutures was covered with

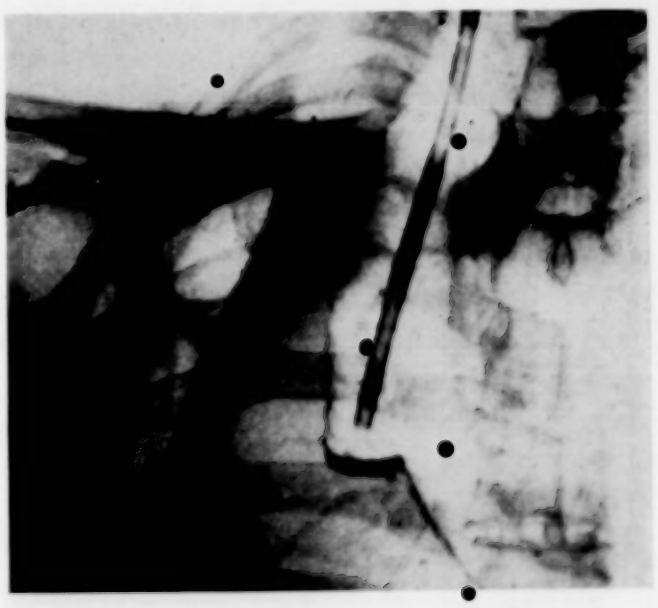


FIG. 2. Bronchography about 2 months after injury. Abrupt stop of the media in the right main bronchus 1 cm from carina.

Loosli, Adams & Thornton, 1949). These authors could show in animal experiments that a complete closure of a bronchus will result in a totally atelectatic lung, but that this will not be infected or destroyed and that the alveolar epithelium does not undergo any morphologic change. Contrary to this, a partial closure of a bronchus will result in infection and destruction of the lung tissue distally to the stenosis.

It is, of course, of great interest to find to what extent a lung which has been functionless for varying periods of time, can be restored, not only morphologically but also functionally after the repair of the bronchial injury. Such investigations are scarce (Weisel & Jake, 1953; Sauvage, 1954; Krauss, 1955; Matthes, 1955; Razemon & Gernez-Rieux, 1956; Mahaffey, Creech, Boren & De Bakey, 1956; Samson, 1956). Weisel & Jake and Mahaffey, et al. report on a case of traumatic bronchial rupture, where in differential pulmonary function studies the affected lung side had regained a good function capacity. In Weisel and Jake's case it was a matter of a rupture of the right bronchus, where operation was performed 46 days after the injury occurred. Three months after operation the right lung was capable of handling 38 % of the total oxygen uptake (as compared to 53 % normally). Its share of the total ventilation and the total vital capacity was also somewhat reduced. In the Mahaffey *et al.* case there was an interval of 11 years between the time of the rupture of the left main bronchus and its repair. Five months after the successful operation the left lung handled 35 % of the total circulatory oxygen. Its share of the total ventilation was practically as great, while its share of the total vital capacity, on the other hand, was smaller.

From these observations it appears that, despite the time interval, surgical therapy may result in a good functional capacity of the lung (on the side of the injury).

In Samson and Krauss's case the lung showed good restoration apart from the circulatory oxygen, which remained considerably reduced. Krauss mentions the possibility of a residual injury of the alveolar epithelium.

As cases published on pre- and postoperative lung function tests are rare, we considered the following case, which has been treated and tested at the thoracic surgical clinic in Malmö, to be of interest.

CASE REPORT

In July, 1956, a 43-year-old farmer, previously healthy, fell 3 meters from a hay wagon. He landed on the right side of his head and thorax. He was not unconscious but felt afterwards that his chest was "blown out". He was immediately brought to the nearest hospital where a pronounced stridurous respiration and lip cyanosis was found. A moderate subcutaneous emphysema was palpated over the right anterior chest.

Immediate chest X-rays did not show any signs of rib fractures, but showed a total collapse of the right lung and shifting of the mediastinum to the left. Continuous suction was applied in the right pleura space, resulting, in a few days, in the extraction of a large quantity of a very sanguineous exudate.

During the course of the next 7 weeks the right lung re-expanded but collapsed completely on three different occasions in spite of continuous suction. It finally appeared evident that there was a big communication between the lung and pleura cavity and the patient was transferred to the dept. of Thoracic Surgery in Malmö.

DISCUSSION OF LUNG FUNCTION RESULTS

In the above case, surgery was resorted to about 2 months after injury. A complete rupture of the right main bronchus was found and re-instituted by an end-to-end anastomosis. The post-operative course was entirely satisfactory. The patient, whose pre-operative condition was poor, improved rapidly. His poor condition was probably due to a venous-arterial shunt, as indicated by the fairly marked cyanosis and slight dyspnoea at rest. The *spirometric investigation* showed that the lung volume was reduced by almost 50 %. The alveolar ventilation seemed almost normal. Owing to the general condition of the patient, no testing of the maximal breathing capacity and the maximal expiratory volume could be made. The lung function was followed up by spirometry and broncho-spirometry, on four occasions, i.e. 3 weeks, 6, 7 and 27 months post-operatively. Table 1 shows that it has been possible through spirometry to find a gradual increase of the total capacity of the lungs (TLC) which, at the last examination 27 months after operation, amounts *to 85 % of the estimated normal value*. The vital capacity (VC) at the same examination amounts to about 3.7 l, corresponding to about 81 % of the normal value estimated for the patient. These values are within the limits of the normal variations. The residual lung volumes (FRC and RV) still hold a somewhat larger share of the total capacity of the lungs than normal. Even as early as 3 weeks post-operatively the maximal breathing capacity (MBC) was 68 l/min. (57 % of the estimated normal value), and after 14 months the maximal breathing capacity was normal (89 %). However, the MBC was slightly reduced in the last check-up 27 months post-operatively. Similarly the maximal expiratory volume (MEV) has been improved and now constitutes 3.24 l during the first second, or 98 %. Simultaneously with the improvement of MBC and MEV the lung clearance index has fallen from 12.8 to 8.9, between the first and last postoperative examinations,

TABLE 1. Results of pre- and post-operative spirometric examinations.
(Figures in parentheses indicate the percentage of estimated normal values.)

	1956 (operation 19/9) 15/9	10/10	1/3 1957	22/11 1957	8/1 1959
TLC, in l	3.7 (53)	3.5 (50)	5.7 (82)	6.0 (87)	5.9 (85)
VC, in l	2.4 (52)	2.2 (49)	3.5 (77)	3.4 (75)	3.7 (81)
FRC, in l	2.04	2.2	3.9	4.2	3.6
RV, in l	1.5	1.2	2.2	2.6	2.2
FRC/TLC, %	55.6	63.0	69.2	70.4	60.9
RV/TLC, %	35.1	35.5	38.7	43.4	37.4
MBC, l/min.	—	68 (57)	90 (76)	118 (99)	90.4 (78)
MEV (1 sec.), in l	—	2.2 (97)	1.5 (94)	3.4 (98)	3.24 (98)
Lung clear. index	9.3	12.8	9.4	9.1	8.9
Art. p_{O_2}		82 mm Hg			93 mm Hg
Art. p_{CO_2}		40 mm Hg			37 mm Hg

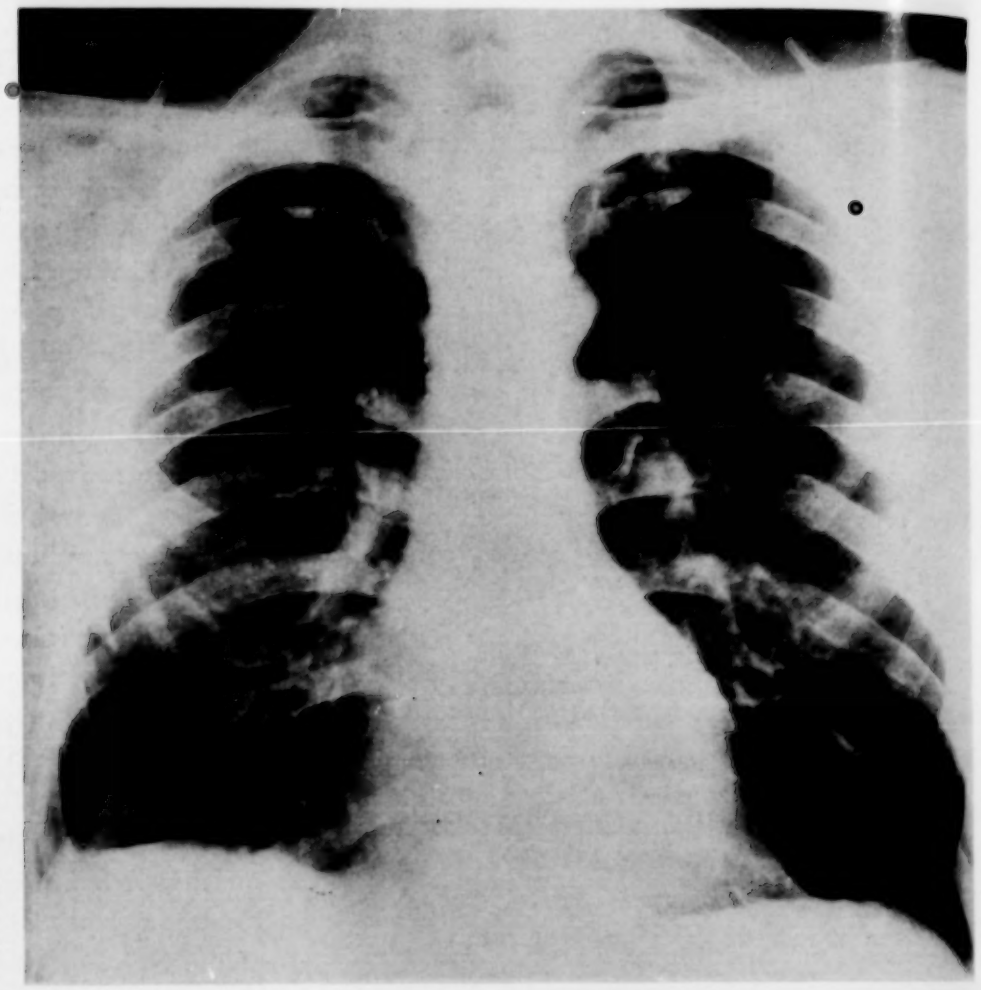


FIG. 3. Lung roentgenogram 27 months after operation. No visible pathology in the lungs.

adjoining soft tissues with isolated sutures of stainless steel wire so that the lumen was properly re-established. The lung was re-inflated by the anaesthetist and in 10–15 min., after removal of some rinds on its surface, was fairly well expanded. Two rubber catheters for continuous suction were placed in the usual manner in the pleura cavity and the chest was closed.

The postoperative course was uneventful and a dramatic improvement appeared in the general condition of the patient. Three weeks post-operatively the patient could walk up three flights of stairs without difficulty. He resumed his usual work as a farmer 3 months after operation. Follow-up examinations 5, 14 and 27 months post-operatively revealed continued good health (Fig. 3).

Post-operative bronchography shows good anastomosis (see Fig. 4). Medially one can see a small lump at the site of the anastomosis.

The right lung's function was observed in 4 post-operative check-ups (see Tables 1 and 2).



FIG. 4. Post-operative bronchography. Good passage through anastomosis. The anastomosis site is indicated by a step-like formation seen medially.

Although traumatic bronchial rupture is not very common at present, the increasing rate of traffic accidents will increase its frequency in future. In severe injury to the chest it is therefore of great importance always to bear in mind the possibility of such a diagnosis.

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TABLE 2. Results of post-operative bronchospirometric investigations.

Broncho-spirometry	TLC R, % of total	VC R, % of total	FRC R, % of total	FRC/TLC R	FRC/TLC L	RV/TLC R	RV/TLC L	Min. vent. R, % of total	Lung-clearance index R	Lung-clearance index L	O_2 uptake R, % of total
10/10 1956	26	17	40	84.5	45.2	53.6	19.6	17	14.0	9.5	21
1/3 1957	—	43	—	—	—	—	—	42	—	—	47
22/9 1957	42	43	44	78.3	72.5	55.7	56.0	40	11.5	6.8	55
8/1 1959	54	44	58	80.1	66.3	63.8	46.3	44	8.4	7.6	53

which shows a normal gas distribution in the lungs. Analysis of the arterial blood gases was performed during the first and last post-operative examinations. The results from the first examination showed an insignificant lowering of the arterial oxygen tension, while the carbon dioxide tension was normal. At the last examination the values were normal.

The improvement after operation can be even better analyzed by a *differentiated lung function analysis with bronchospirometry* (Table 2). The *volume of the right lung* has increased continuously and its share of the total now constitutes 54 % (normal value 53 %). The last examination also revealed that the two residual lung volumes (FRC and RV) held a definitely larger share of the capacity of the right lung than was the case in the left lung.

A striking improvement was obtained in *the right lung's share of the total ventilation*, which has increased from 17 % to 44 % in the sitting position. At the same time the efficiency of the ventilation has increased, as indicated by the lowered values of the lung clearance index. The share of the right lung in the minute volume is normal in supine, right and left lateral position, but somewhat reduced in the sitting position.

The oxygen uptake of the right lung has gradually increased from 21 % of the total to its normal share between the first and final examinations, respectively, indicating that the right lung circulation was normal.

The functional analyses thus definitely proved that improvement had taken place. The analyses also showed that the improvement was made gradually and continued for a long time post-operatively.

SUMMARY

A brief survey of the literature on traumatic bronchial rupture is presented.

Presentation of a case of traumatic complete rupture of the right main bronchus, which was repaired by an end-to-end anastomosis of the bronchial stumps. The operation was performed two months after the accident and the post-operative course was uneventful.

The patient was followed up on several occasions. Three months after operation he could resume his usual work and at the final check-up 27 months post-operatively, he was in fit condition subjectively and objectively.

The patient's respiratory status has been followed with spirometries and bronchospirometries 3 weeks and 5, 14 and 27 months after operation. These investigations showed a gradual course of improvement of the function of the right lung. Normal right-lung volume and circulation was found on final examination. Its ventilation conditions were also practically normal.

ACTA CHIRURGICA SCANDINAVICA, SUPPL. 245: 151–156, 1959

From the Department of Thoracic Surgery and the Department of Roentgenology, University Hospital, and the Department of Pathology II, University of Uppsala, Sweden.

Ciliated Epithelial Cyst of the Oesophagus

Case Report

V. O. Björk, B. Fors and H. Lodin

Ciliated epithelial cysts of the oesophagus are very uncommon. Fifty-one cases have been reported in the literature. Although it is probable that many more such cases have been operated upon than the fourteen reported in the literature, most thoracic surgeons will see only an occasional case. Creech & De Bakey (1954) are in fact the only surgeons who have reported two operated cases of ciliated epithelial cyst of the oesophagus. Sauerbruch (1931) was the first to remove an oesophageal cyst. We recently operated upon a patient with a circumscribed tumor located in the right anterior wall of the lower third of the oesophagus. The preoperative roentgenological diagnosis was an intramural oesophageal tumor, probably a leiomyoma. However, the tumor proved to be a ciliated epithelial cyst of the oesophagus. Because of the rarity of oesophageal cysts and the diagnostic difficulties we wish to relate the case.

CASE REPORT

A 61-year-old woman had been complaining for a year of a lump of mucus in the throat of which she was not able to get rid. The symptoms were most pronounced when she was lying down and in the mornings. She experienced no difficulties in swallowing.

Radiological examination showed a tumor, the size of an egg, protruding into the oesophageal lumen ten centimeters above the cardia, see Fig. 1. The tumor could also be detected on previous radiograms taken three years earlier. The roentgenological diagnosis was an intramural tumor, probably a leiomyoma.

In December 1958 a thoracotomy was carried out through a right postero-lateral incision. Retraction of the lung anteriorly revealed a rounded mass within the mediastinum at the level of the ninth thoracic vertebra, see Fig. 2. The tumor was situated in the right anterior wall of the oesophagus and could not be shelled out as an ordinary leiomyoma. Mobilization of the tumor necessitated excision of portions of the muscular wall over a large area. For biopsy an incision was performed and revealed a cyst with greyish-brown viscid fluid. On the basis of a quick frozen section malignancy was excluded. The cyst was then removed by blunt and sharp dissection, there being no communication with the lumen of the oesophagus. As there was a rather large defect after the cyst, reapproximation of the musculature could only be carried out under considerable tension.

The convalescence was uneventful and the symptoms disappeared. At the follow up the roentgenological examination showed a broad-based diverticulum of the oesophagus at the level of the extirpation, see Fig. 3.

Pathologic report: Grossly the specimen presented

traumatique de la bronche souche droite. Opération reconstructive. *Lyon Chir.*, *53*: 438, 1957.

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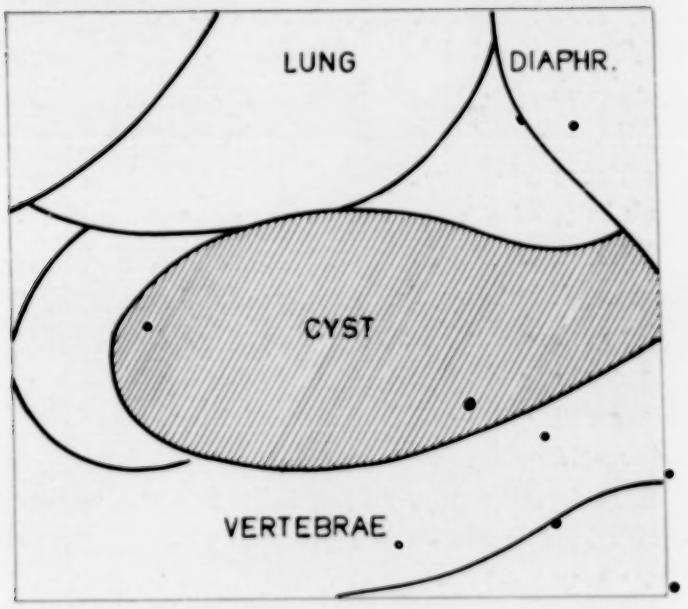


FIG. 2. The oesophageal cyst during the operation.

Another explanation of the development of these cysts is that they are derived from tissue fragments separated off at the detaching of the trachea from the gut, or oesophago-tracheal fistulas occluded at the ends, or rudimentary lung anlagen. These views are based on the epithelial type and the occurrence of cartilage in the cyst wall.

Both these theories may be accepted. We assume, however, that when hyaline cartilage is found the cyst is bronchogenic, and when there is a real muscular coat in two layers, and especially, as Ranström has emphasized, when there is a muscularis mucosae, the origin is in the oesophagus. The definite oesophageal wall has a muscularis mucosae and mus-

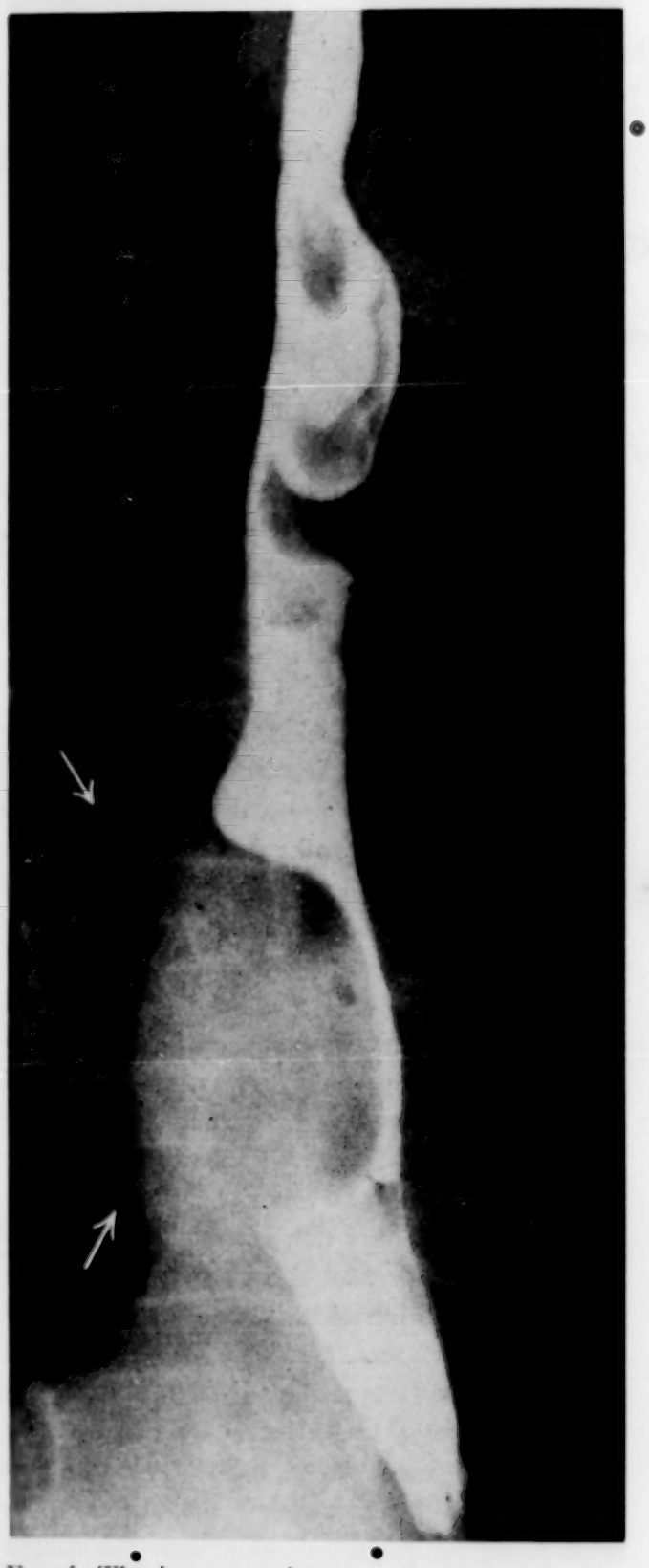


FIG. 1. The intramural tumor, the size of an egg, protruding into the lumen of the oesophagus. The operation revealed a cyst.

a smooth external surface of grey-brown color. The wall of the lobulated irregular cyst varied from one to two millimeters in thickness and was trabeculated. Microscopically the inner lining consisted of a ciliated pseudo-stratified mucus-producing columnar epithelium, see Fig. 4. In places the epithelium was replaced by a hyaline fibrous tissue. Beneath the epithelium there was a loose connective tissue and in a few places a thin muscular coat partially resembling a muscularis mucosae, see Fig. 5. Outside of this, partially separated, followed a smooth musculature arranged in two layers, where the fibres ran almost perpendicular to each other, see Fig. 6. In the places with evidence of a mucosa with a muscularis mucosae and a submucosal layer no glandular formations were seen.

DISCUSSION

Leaving cystic teratoma and ciliated epithelial cyst of the thymus out of question, there are two main groups of ciliated epithelial cysts of the mediastinum:

1. Bronchogenic cysts, thought to be derived from a pinching off of buds from the primitive trachea and usually found at the level of the tracheal bifurcation in the posterior part of the mediastinum.
2. Ciliated epithelial oesophageal cysts, found within the muscular wall of the oesophagus or in intimate connection with it. This group, which is less common, is a subgroup of a larger one containing also other cysts derived from the alimentary tract, with linings of gastric or enteric type.

Oesophageal cysts are thought to develop from the diverticula normally found in the primitive oesophagus during the second foetal month in the twenty millimeter stage (Ranström, 1945; Schlumberger). At this stage both oesophagus and trachea are lined with ciliated epithelium. In rare cases there persists a communication with the lumen of the oesophagus (Schlumberger).



FIG. 6. The complete cyst wall with its different layers: the mucosa with the epithelium and the thin muscular layer resembling a muscularis mucosae, the thin submucosa, and the muscularis propria with its two perpendicular layers (× 60).

cularis propria, but the definite tracheal wall has no muscularis mucosae and a muscularis propria only in the posterior wall.

The cysts of the oesophagus are most frequently found in the lower third of the latter, as there is then a rapid elongation of the oesophagus.

As regards the diagnosis, we cannot see any possibility of distinguishing a real oesophageal cyst from other intramural tumors such as leiomyomas unless a puncture of the cyst is performed, and this method cannot be recommended. In spite of the benign appearance of the tumor on the radiogram a malignant tumor cannot be excluded (Gockel, 1959; Goldmann, Marshalk & Friedmann, 1952). A cystic diverticulum may be detected by radiological examination.

The symptoms are vague. Sometimes the cyst interferes with swallowing. In some instances there may be cardial symptoms, disappearing after extirpation (Creech & De Bakey, 1954).

As a definite diagnosis is practically impossible by other means than surgical exploration, this measure is indicated even in the absence of symptoms. During the operation one must take care to excise as little as possible of the oesophageal musculature once malignancy is excluded. Otherwise there will be too much tension on the reapproximating sutures of the musculature, resulting in a diverticulum. In our case the multilobulated cyst made a rather extensive resection necessary. A reinforcement of the approximated oesophageal musculature by a pleural flap or by lung tissue was considered during the operation, but was thought to be unwise because of the risk of scarring and stricture formation, which are more dangerous than a broad-based diverticulum.

SUMMARY

A comparatively rare case of an operated ciliated epithelial cyst of the oesophagus is reported. The theories of the genesis are briefly reviewed and the diagnosis discussed.

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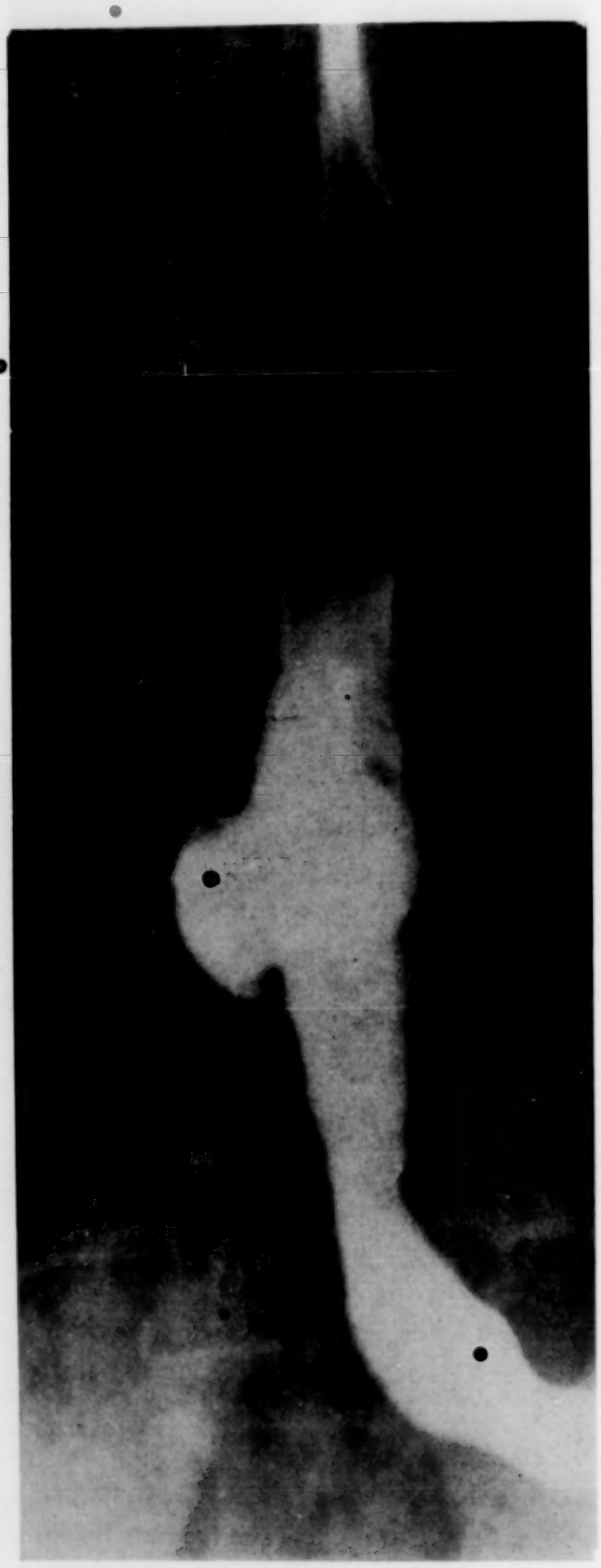


FIG. 3. The postoperative radiogram with the broad-based diverticulum at the level of the extirpation.

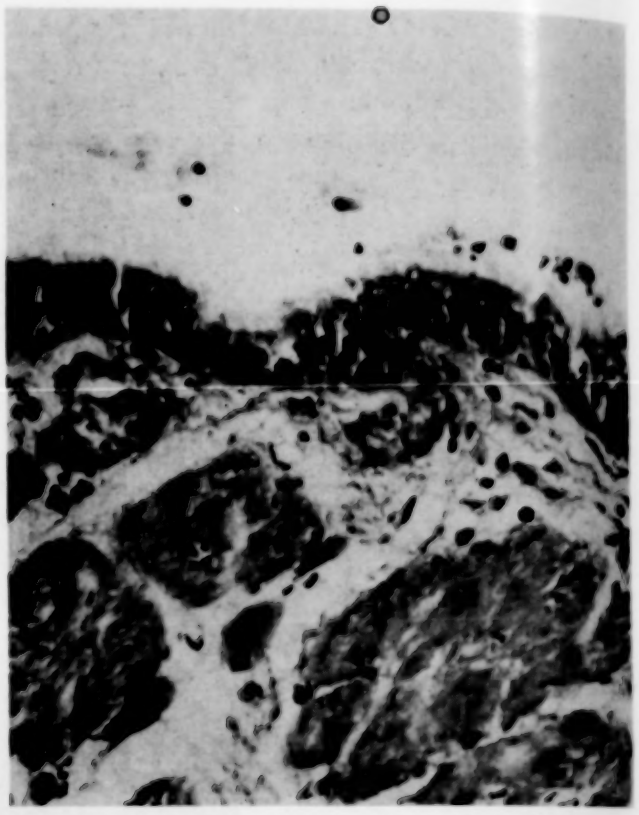


FIG. 4. The cyst wall with the ciliated pseudostratified mucus-producing columnar epithelium ($\times 600$).

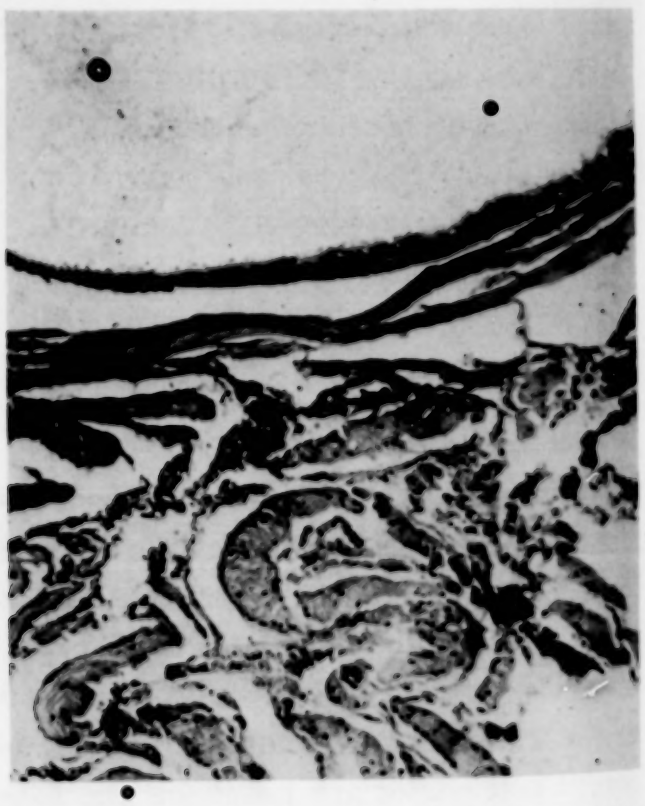


FIG. 5. A part of the cyst wall with a thin muscular layer beneath the epithelium resembling a muscularis mucosae ($\times 200$).

ACTA CHIRURGICA SCANDINAVICA, SUPPL. 245: 157–161, 1959

From the Surgical Department A of the University Hospital, Oslo, Norway

Carcinoma of the Lower Portion of the Esophagus

LEIF EFSKIND

Even though in the course of the past fifteen years surgery of the esophagus has become a steadily decreasing problem from a technical-surgical point of view, carcinoma in this organ still presents many therapeutical problems. This is also reflected in surgical literature. The enthusiasm of the initial years has gradually veered to a certain degree of pessimism. As in medicine generally it may probably be stated that the truth lies between the two extremes.

The main problem is that the first symptom presented by these patients, dysphagia, does not manifest itself until until late in the course of the disease. Many of these patients, therefore, are not accessible to radical surgery. A further problem is that the spread of tumor cells occurs early. Thus, more than two-thirds of the patients who undergo radical operation have metastases in the regional lymph nodes (Fig. 1). Another matter to be emphasized in this connection is that the spread to the lymphatic system is not local as a rule, involving also the lymph nodes around the coeliac axis, the lymph nodes on the upper portion of the lesser omentum and those in the supraclavicular fossa. In other words, at an early point of time the spread to lymph nodes includes the region from the upper abdominal area to the neck. This applies even though the carcinoma is localized to the most different parts of the esophagus.

A third therapeutical problem is the rapid spread of the tumor tissue in the submucous lymphatics of the esophagus proper (Fig. 2). Thus, microscopical secondary nodules are found frequently at a great distance from the primary growth. This spread is most marked orally to the tumor. This is experienced also with carcinoma of the cardia of the stomach, which frequently has a considerable tendency to spread upwards in the esophagus.

A fourth problem is the fact that many of the publications on the results of surgical and radiological treatment of esophageal carcinoma are only slightly comparable. There is particularly one circumstance which is apt to cause confusion in the evaluation of the different materials, viz. that many authors include in their esophageal material also carcinoma of the cardia, which frequently differs greatly from the squamous cell carcinoma of the esophagus, with regard to histology, conditions of spread, and therapeutical technique.

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TABLE 1. Material 1948–58.

Inoperable	100
Radically operated	101
Total	201

wide. The age in the operative group has varied between 47 and 83 years. A previous heart infarction has not been regarded as contra-indication against surgical treatment. Neither has the radiological extent of the tumor been any decisive contra-indication against operative treatment. Surgical exploration has been undertaken in 38 patients of the inoperable group.

The surgical intervention has been performed by a left-sided thoraco-abdominal exposure of the stomach and the esophagus. Great weight has been attached to a radical dissection of the lymph nodes around the coeliac axis. Together with this dissection the lesser omentum has been removed on the upper portion of the stomach from the point of the left gastric artery up to the cardia. This is of great significance in order to obtain a radical operation as the material frequently has demonstrated metastases to lymph glands at these sites.

It has been maintained by several authors that carcinoma localized to the mid-esophagus is more frequently inoperable than carcinoma of the lower esophagus. The present material submits no definite proof of this, the percentual operability having apparently been about the same in both sites (Tables 2–4). The main cause of the inoperability, however, is different for carcinoma in the lower portion of the esophagus. The local invasion gives a higher incidence of

TABLE 2. Reasons for inoperability.

Local invasion	47
Distant lymph node metast.	23
Peritoneal or pleural metast.	9
Hematogenous spread	20
Cardiopulmonary insuff.	2
Total	101

TABLE 3. Radically operated.

Operation	Number	Mortality
Supraaortic anastomosis	52	5
Infraaortic anastomosis	49	6
Total	101	11 (10.9%)

TABLE 4. Chief causes of death.

Anastomosis leak complic.	6
Pulmonary embolism	3
Hematemesis	1
Cardiac complic.	1
Total	11

inoperability for carcinoma of the mid-esophagus than for the other group, while on the other hand the carcinoma of the lower portion of the esophagus has a more frequent invasion of retroperitoneal lymph nodes, which is one of the causes of inoperability. According to our material, however, invasion of the aorta has only rarely constituted any decisive obstacle to the operation. Infiltration of the main bronchus is much more frequently responsible for the inoperability. This means that in all cases of carcinoma of the mid-esophagus the left main bronchus should invariably be examined by endoscopy. The size of the tumor, as estimated according to the radiographic findings, is of no decisive importance as a sign of inoperability, and should by

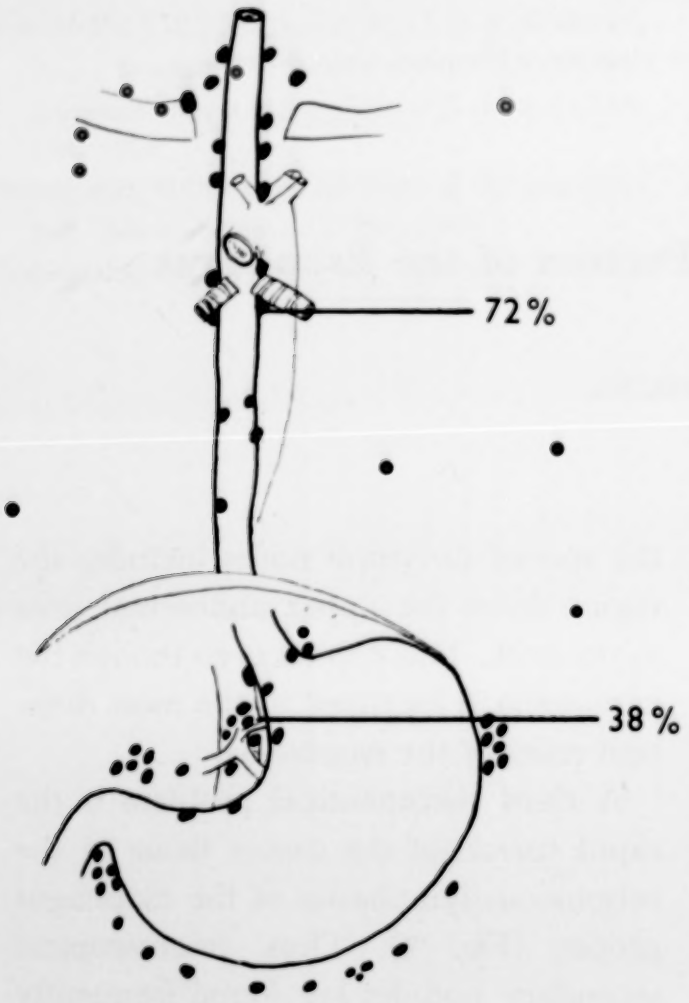


FIG. 1. Lymph node metastases in 101 cases of carcinoma of the esophagus treated with radical surgery.



FIG. 2. Lymphatic spread in esophagus 7 cm from the primary tumor.

Further there is one factor which adds to the difficulty of analyzing the various publications, namely that the majority of the investigators have accepted a schematical classification of the esophagus in different sections. It is obvious that a malignant tumor does not heed such a schematic distribution, and the tumor, when it is diagnosed, infiltrates more than one of these sections. Thus, in the present material it has been observed that the majority of the carcinomas have been localized to mid-esophagus including as well a portion of the lower third of the esophagus. In this material, therefore, the site of the tumor will be classified on the basis of a clinico-therapeutical principle, namely the level of the anastomosis at the surgical intervention, viz. whether it has been placed above or below the aortic arch. In other words, this indicates that the very low carcinomas of the esophagus form a separate group, while carcinomas of the mid-esophagus and the upper portion of the lower third form another separate group.

MATERIAL

In the course of the period from 1948 to 1958 a total of 201 patients have been admitted to our department suffering from carcinoma of the lower portion of the esophagus, 101 of whom have been subjected to radical operation (Table 1). The indications for operation have been

As far as the late results in the operated patients are concerned, the two other factors seem to be of considerable significance in the present material: the distant lymphogenous spread, and the spread in the lymph vessels of the esophagus.

The late results for these patients are not at all favourable. Here, as in carcinoma therapy otherwise, however, it is imperative to accept the low figures and not to be incited to negativism, but rather to let them be an incentive. The chance of improving the results should be present even in the orthodox procedures of surgery and irradiation. An earlier diagnosis will serve to make the local invasion as well as the lymphogenous spread less extensive. In order to get the best possible control of the organic and lymphogenous spread it is necessary to make the operation as radical as possible, including a precise dissection of lymph nodes and lymphatics from the coeliac axis, along the lesser curvature of the stomach, and upwards to the groups of glands above the aortic arch. The local spread inside the organ has to be controlled by making the resection as high as possible. The result will be that in practically all cases of carcinoma the resection has to be so high that a supra-aortic anastomosis will be required.

The palliative treatment of carcinoma of the esophagus is a problem in itself. Several methods have been suggested for surgical treatment of the chief symptom of the patients, the dysphagia. All these methods, however, are encumbered with a rather high rate of mortality. It is our experience, however, that irradiation therapy is very effective in giving the patient considerable relief from pain and from discomfort of stenosis. Only a few of the patients in the present material, who have been treated with irradiation, have got a nutritional fiistula in the terminal stage.

SUMMARY

An account is given of 101 patients with squamous epithelial carcinoma of the esophagus, who have been treated radical-surgically. The rate of operative mortality has been 10.9 %. The survival time after three years is 16 % and after five years 10 %. The material has been classified into two groups, one comprising patients with supra-aortic treatment, and one including patients with infra-aortic treatment. Neither the rate of operative mortality, the operability, nor the late results have varied significantly in these groups.

Due to the lymphogenous spread outside the esophagus as well as to the intramural spread, high resection is recommended, except for the carcinomas located close to the cardia.

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no means restrain the investigator from surgical exploration.

Metastases to the tributary lymph glands play a distinct, but not decisive role for the prognosis. Such local metastases have been found in 40 % of the patients surviving after three years. The distant metastasization, however, plays a far more decisive role. Only two of the patients who had metastases to the lymph nodes around the coeliac axis have a period of survival of three years or more. Metastases to the lymph nodes behind the clavicle have been a definite sign of inoperability.

Extensive lymphogenous spread in the esophagus wall generally indicates a poor prognosis. When such spread has been demonstrated in the margin of the resection area, no patient survives more than three years. The result of this has been that at present time we resect as high up on the esophagus as the extent of the mobilized stomach permits. Even for the low esophageal carcinomas, therefore, we have more and more changed to high resection with supra-aortic anastomosis.

Invasion of the stomach by lower esophageal carcinomas appears to occur to a relatively small extent, whereas the cardia does not seem to form any barrier against spread from stomach to esophagus. This rarely creates technical difficulties due to an essential shortening of the gastric specimen.

As far as survival time is concerned for the patients subjected to radical operation, it will be observed that the majority of patients succumb within two years postoperatively. However, those who reach a survival time of three years, have a relatively great chance of survival after five years (Table 5). This applies also to our late results in patients subjected to radical operation for high gastric carcinoma (Table 6). Some of our patients have been treated with irradiation postoperatively, though this seems to have played no essential role in the prognosis.

TABLE 5. Survival.

> 3 years	12 of 75	16 %
> 5 years	7 of 69	10 %

TABLE 6. High gastric carcinoma.

No.	Op. mortality	Alive 3 yrs.	Alive 5 yrs.
352	13.6 %	18.4 %	12.2 %

COMMENTS

Our experience with surgical treatment of carcinoma localized to the cervical portion of the esophagus is so poor that we have commenced treating these patients exclusively with irradiation. The present material therefore comprises carcinoma of the lower part of the esophagus.

Considering the pathological-anatomical and clinical findings, there are three factors which are significant in the prognosis of patients with carcinoma of the esophagus.

The local invasion is one of the main factors with regard to the inoperability of these patients, and is therefore an essential hindrance to radical surgical treatment.

The dilatation proximal to the stenosis may be marked; this often causes aspiration with resulting cyanosis and pulmonary complications. Peptic esophagitis and mucosal destruction may lead to hemorrhage and anemia.

Roentgenologic examination with contrast medium and esophagoscopy lead to a definite diagnosis, and allow visualization of the site and extent of the stricture. Information is also obtained regarding the state of the mucosa and the existence of peptic esophagitis, as well as the eventual presence of gastric mucosa in the lower part of the esophagus.

TREATMENT

Conservative treatment, consisting of a fluid diet, spasmolytics, antibiotics and daily irrigations, may relieve the symptoms in certain mild cases, by decreasing the peptic esophagitis and spasm. However, this treatment alone often leads to marked undernourishment and underdevelopment.

Gradual dilatation has proved successful in many cases (Gross, 1953; Terracol & Sweet), and is used even when a short, web-like membrane is present. This procedure is, however, associated with a relatively great risk of perforating the esophagus.

Short strictures at different levels of the esophagus have been found amenable to excision and end-to-end reconstruction with or without plastic repair (Gross, 1948; Sandblom).

Paine (1951) found, in a study of the American literature, 16 cases of severe congenital stricture which had required resection and various kinds of reconstruction, with fairly good results in 15. Esophagogastrostomy had been performed in 13 of the patients, and in two personal cases. Paine stated that his own cases had, however, presented a number of postoperative problems—especially in the early postoperative period—in the form of frequent regurgitation of the gastric contents into the pharynx.

Gross (1953) reported that it was necessary to resort to partial esophagectomy and end-to-end suture in only 5 cases in a series of 38, and that no extensive reconstruction was required in any of them.

Holinger, Johnstone, Potts & daCunha (1954) had a series of 43 cases of benign stricture; excision of the stricture and esophagogastric anastomosis had to be performed in 5 of them. Postoperative stricture appeared in the anastomosis in four of these patients, and necessitated repeated dilatation. No postoperative complications occurred in the fifth case, in which the anastomosis was made above the aortic arch (as in my case). Allison, Wooler & Gunning (1957) stressed the drawbacks of esophagogastric anastomosis—regurgitation, stricture formation and inhalation of stomach contents into the lungs during sleep—and recommended esophagojejunogastrostomy instead. They used this technique in seven cases (pyloromyotomy was done as well in three cases); six patients survived and became asymptomatic.

Now that antethoracic cutaneous reconstruction of long esophageal defects has fallen into increasing disuse, the choice lies between using the stomach, jejunum and colon for esophageal repla-

ACTA CHIRURGICA SCANDINAVICA, SUPPL. 245: 162–168, 1959

From the Department of Surgery, Centrallasarettet, Örebro, Sweden

Congenital Stricture of the Esophagus Treated by Excision and Esophagogastrostomy

Report of an Unusual Case

BENGT GÖTHMAN

ANATOMY

The most common congenital anomaly of the esophagus is atresia with or without a tracheo-esophageal fistula. This condition requires immediate surgical correction if the infant is to survive. Another congenital malformation, although it is rare, consists of stricture or stenosis, which only partially blocks esophageal passage, and therefore does not cause any problems until later in childhood (Lisa & Taylor, 1948; Sandblom, 1949; Gross, 1953).

The rare congenital stricture or stenosis is characterized by narrowing of a segment of the esophagus, usually in its lower third, without initial inflammatory changes or fibrosis. The stenosed segment sometimes consists of a diaphragm-like or valvular formation, in which case the secondary lesions of the wall are less severe. The longer stricture may extend from the tracheal bifurcation, seldom higher, as far as the cardia. Inflammatory lesions and fibrosis develop, with a tendency to shrinkage of the esophageal wall and constriction of the lumen. In addition, the esophagus becomes dilated proximal to the stenosis, and this condition soon demands medical and surgical intervention (Humphreys, 1958; Terracol & Sweet, 1958).

CLINICAL FEATURES

Children with congenital stricture of the esophagus generally have symptoms which appear very early in life, and the anomaly is usually detected during the first or second year. Even in cases in which it is not diagnosed until later in childhood, there is generally a history of symptoms dating back to infancy (Gross, 1953). The symptoms are likely to make their appearance when the child progresses from fluid to semisolid or solid food. The dominant features are regurgitation at practically every meal, and loss of weight or failure to gain weight. Profuse secretion of mucus, dysphagia and pain are also present. The more severe the stenosis, the earlier and more severe are the symptoms.

The dilatation proximal to the stenosis may be marked; this often causes aspiration, with resulting cyanosis and pulmonary complications. Peptic esophagitis and mucosal destruction may lead to hemorrhage and anemia.

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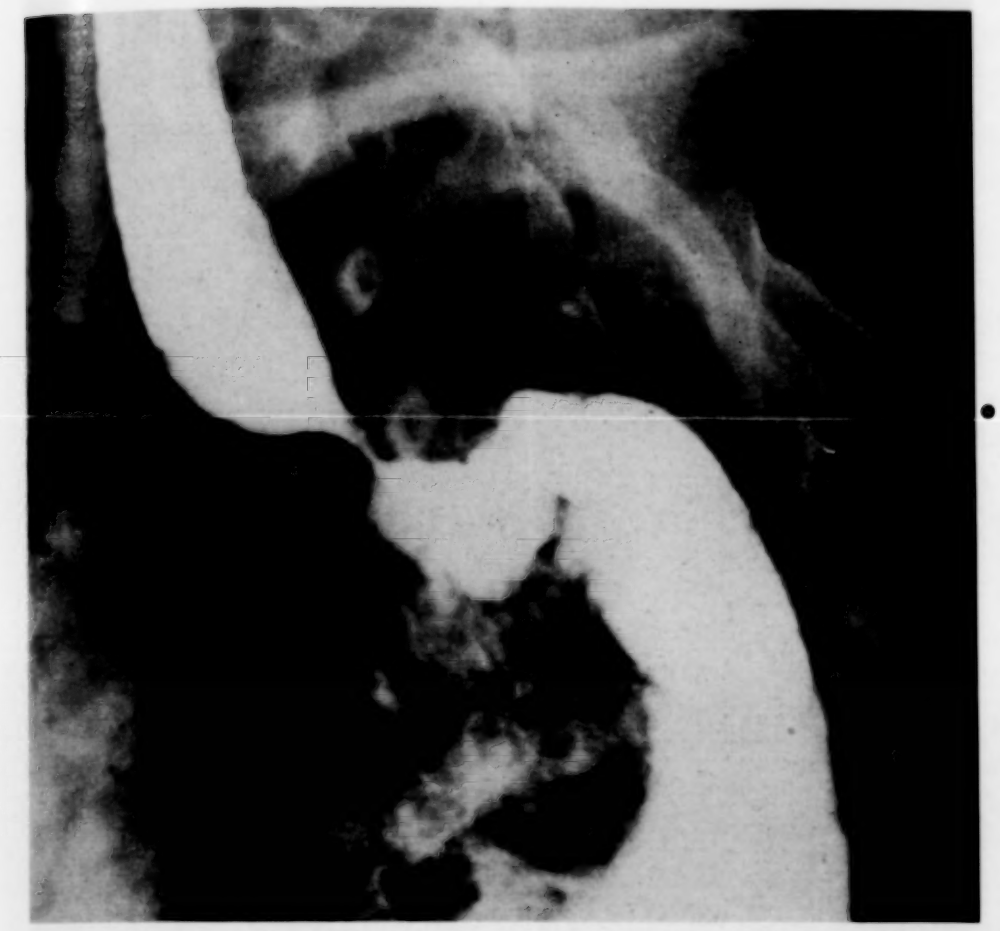


FIG. 2. One month after operation, consisting of excision of the stenosed segment and esophagogastrostomy. A stricture has developed in the anastomosis.

part of the esophagus, starting at the level of the aortic arch (Fig. 1). The mucosal relief was obliterated in the stenosed segment. Marked prestenotic dilatation was visible in the proximal part of the esophagus. Hiatal hernia and so-called brachyesophagus were also present.

In view both of the severe anatomic changes, i.e., a marked, long stricture with deep-seated esophagitis and mucosal destruction, and of their effects—underdevelopment, undernutrition and severe anemia—further conservative treatment was considered unfeasible. The patient was therefore referred for surgical treatment.

Operation was performed in July 1956. It consisted of excision of the esophagus from below the level of the aortic arch down to and including the cardia, mobilization and drawing up of the stomach into the left thoracic cavity, and esophagogastric anastomosis in front of the aortic arch. The part of the esophagus above the stenosis was grossly dilated and thick walled. The stenosed segment had a thick, greatly indurated wall and was difficult to mobilize.

Microscopic examination showed total destruction of the mucosa; marked inflammatory changes were present in the submucous and muscular layers, extending into the serous membrane. The muscular layer was thickened, and contained numerous nervous-tissue elements. Gastric mucosa with inflammatory lesions was present in the distal part of the esophagus.

The postoperative course was initially completely uneventful, but after a month the anastomosis became too narrow (Fig. 2) and necessitated cautious probing. Since then, the size of the anastomosis has remained unchanged, and no dilatation has been required. At the time of writing, the patient can eat any kind of food and never vomits. He has developed well, has no anemia and has gained 9 kg in weight during the observation period, which is almost three years. Roentgenologic examination now shows a satisfactory anastomosis with no dilatation above it (Fig. 3). No regurgitation can be provoked, even if roentgenologic examination with contrast medium is performed with the child's head hanging down. The drawn-up stomach seems to have narrowed, and takes up little place in the thorax.



FIG. 1. Preoperative examination. Boy aged 3 years 8 months, with congenital stricture of the esophagus, hiatal hernia and so-called brachyesophagus.

cement (Yudin, 1944; Sweet, 1946; Robertson & Sargeant, 1950; Holinger *et al.*; Allison *et al.*; Terracol & Sweet). These operations are nevertheless procedures of great magnitude, and have both advantages and drawbacks. Moreover, opinions are at variance regarding the merits of the different methods, and in the small series hitherto reported, postoperative and late complications have been described, in the form of peptic esophagitis, stricture and nutritional difficulties.

An account is given in the following of an unusual case of long, congenital stricture of the esophagus, with severe inflammatory changes and hiatal hernia, as well as so-called brachyesophagus, probably of secondary origin. The case was treated with good results by radical excision of the lower part of the esophagus, and esophagogastrostomy at the level of the aortic arch.

CASE REPORT

A boy, aged 3 years 8 months, was admitted to the Paediatric Department of our hospital in June 1956, on the grounds of nutritional difficulties, vomiting and severe anemia. Since the age of 18 months, he had invariably vomited on eating solid food, and had a profuse secretion of mucus after every meal. He had a history of repeated infections, with cough and pulmonary complications. On admission, he was greatly debilitated, emaciated (weight 12.5 kg) and had severe secondary anemia. Roentgenologic examination disclosed a long, high-grade stricture of the lower

If a valve-like mechanism can be produced in the actual anastomosis, and regurgitation prevented, no late complications seem to occur, as in one case reported by Holinger *et al.*

In the present case, such a "valve" has apparently been formed (Fig. 3). This is due to the actual anastomosis over-riding the aorta in a suitable way, which evidently prevents any regurgitation, with resulting peptic esophagitis and postoperative stricture.

In recent years, numerous reports have been published of esophageal reconstruction with an isolated loop of jejunum or colon in cases of tumour or other severe diseases of the esophagus. On the other hand, there seems to be little experience of this type of reconstruction in stricture of the esophagus in children. Allison *et al.* have stated emphatically that esophagojejunogastrostomy is the most suitable procedure, and often complement this operation by pyloromyotomy. Doubts as to the ability of the mucosa of colon or jejunum to withstand prolonged contact with gastric juice appear to be unjustified (Humphreys), but longer observation periods are required to rule out the possibility of subsequent gastrojejunal or gastrocolic ulceration. Moreover, these types of reconstruction are difficult technically, and a fairly great risk exists of endangering the blood supply of the mobilized intestinal segments by minor errors.

In the present case, the operation was simple from the technical point of view, the postoperative course was practically free from complications, and no pyloromyotomy was necessary. Furthermore—possibly on the grounds of the "valvular mechanism" formed—neither regurgitation, peptic esophagitis nor stricture has developed during the observation period, which is now almost three years.

SUMMARY

An account is given of an operated case of extensive congenital stricture of the esophagus, with hiatal hernia and so-called brachyesophagus. Operation consisted of excision of the stenosed segment, and esophagogastrostomy in front of the aortic arch. It is pointed out that although opinions in the literature are at variance regarding the merits of this method, the results in the present case are highly satisfactory. No late complications have appeared after an observation period of almost three years.

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FIG. 3. 27 months after operation. Satisfactory anastomosis with no dilatation of proximal part of the esophagus. The stomach seems to have become narrowed, and takes up little space in the thorax.

DISCUSSION AND CONCLUSIONS

The management of benign strictures of the esophagus naturally varies according to the etiology, degree and duration of the stricture. Conservative treatment, with or without dilatation, leads to favourable results in most cases, irrespective of whether the stricture is a congenital malformation, is caused by lye, or is of postsurgical nature. But in certain cases with advanced anatomic changes, a radical intervention must be made, and it is then necessary to resort to excision of the stenosed segment, and reconstruction of the esophagus with the use of stomach, jejunum or colon.

Experience of esophagogastric anastomosis seems to indicate that this often leads to postoperative stricture, which requires constant dilatation (Holinger *et al.*; Allison *et al.*). Another objection raised to this method is that if the normal cardia function is removed, peptic esophagitis is apt to arise, with ulceration as a result of regurgitation of the gastric juice. The latter complications are well known, and have often been reported in the literature (Gross, 1953; Watkins, Prevedel & Harper, 1954; Allison *et al.*).

Sweet and Terracol & Sweet have, however, stated that these apprehensions are exaggerated, and that late complications can be overcome. They still recommend use of the method, as being the most appropriate of those now available.

ACTA CHIRURGICA SCANDINAVICA, SUPPL. 245: 169–172, 1959

From the Clinic for Thoracic Surgery, Karolinska Sjukhuset, Stockholm, Sweden

Extensive Esophageal Stricture of Unknown Etiology

TORSTEN SILANDER and ERIC CARLENS

Any inflammatory process in or around the esophagus may cause esophageal stricture. The most common cause of scar stricture is due to swallowing some corroding substance usually lye. Other causes may be due to general infection, conditions with vomiting, for instance, vomiting in pregnancy, reflux esophagitis from peptic ulcers, tumour, etc.

After considering all conceivable etiological factors there still remains a group of cases of unknown etiology.

A number of such cases have been described by Vinson (1931). He points out that ulcer formation in the esophagus must occur more frequently than is usually recognized, but the inflammatory reaction is mainly superficial and the constriction of the lumen, after the healing, is so small that it will not cause any difficulty in swallowing. The swallowing of foreign objects may cause great ulcerations, but Vinson (1931) reported only one case from his material in which a stricture occurred. He also reported that the cardinal symptom of peptic ulcer of the esophagus was substernal pains and burning sensations. If peptic ulcers cause stricture, these cardinal symptoms ought to exist for a longer or shorter period of time before the onset of dysphagia. In an investigation made in 1923 of 186 cases of benign esophageal stricture Vinson found 18 cases or 9.6 % of unknown etiology. Up to January, 1930, he had observed 243 cases of benign stricture and out of these 40, or 16.4 %, were of unknown etiology, implying a remarkable relative increase of cases of unknown origin. The knowledge of this is important, as the cases often show great similarity to, and often are misdiagnosed as, tumour cases. Many of the patients in Vinson's series had been sent to him under the diagnosis of esophageal carcinoma. He presents an illustration which invites consideration, viz., an X-ray picture of a case of benign esophageal stricture. In one of the lungs is seen the pistol bullet by which the patient tried to commit suicide after being informed of the presumed cancer diagnosis and his hopeless prognosis. The 40 patients (17 men and 23 women) were aged 6 to 75. The strictures which were isolated, short and recessive, caused difficulty in swallowing as a first symptom, followed by pains. In three cases the pains were of the same type as in peptic ulcers and two of them had also verifiable duodenal ulcers. In most cases the pains disappeared after dilatation of

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FIG. 1. *Left:* Roentgenogram showing the appearance of the esophageal stricture 7 weeks after illness first appeared. *Right:* Roentgenogram one month after operation (resection of the esophagus and cardia with esophagogastrostomy). The stomach is mobilised into the thorax. The opaque object in front of the stomach is a metal clip applied during the mediastinoscopy.

rium. The patient, who had lost 30 kg, could not swallow his saliva and often woke up at night with violent coughing attacks after aspiration. A rounded density in the left lung was discovered and further investigated. The sputum and guinea-pig tests were negative. Direct puncture of the process, bronchography and mediastinoscopy with lymph-node biopsy did not give any indication of tuberculosis or other infectious disease. Wasserman's test was negative. Numerous attempts at dilating the esophagus were unsuccessful. In connection with these attempts numerous biopsies were made which remained negative as to tumour or a specific inflammation. The density in the left lung was interpreted as being due to aspiration. After one attempted dilatation the patient became feverish with signs of mediastinitis and a small fistula could be seen on X-ray, paraesophagically. On 8 October, 1958, an operation was performed with resection of esophagus from jugulum height to the cardia, the stomach was brought up into the thorax and the fundus anastomosed to the esophageal stump. Histological examination of the excised material showed thick, hypertrophic mucosa with a chronic unspecific inflammation. There were no signs of tumour, fungus or specific infection. An abscess formation was found in the site of the paraesophageal fistula. Two days after the operation the patient could swallow liquids and food. He was also able to be out of bed and gained some weight. Ten days postoperatively signs of leakage from the suture line appeared,

the esophagus and were considered to be caused more by spasm than by active ulceration in the esophagus. The strictures were located in the distal third (3.5 cm or more from the upper teeth row) in more than half of the cases (51). Of the others, 9 were in the upper and 10 in the middle third. The difficulties in swallowing often came insidiously but in one case quite suddenly. Bloody vomiting occurred in 10 patients. All but one case, which had a total stenosis, were dilated.

Butt & Vinson in 1936 reported a series of 3032 post-mortem examinations in which they found esophagitis in 213 cases. They were divided into three groups: Acute ulcerative esophagitis (75.5 % of the 213), sub-acute ulcerative esophagitis (14.5 %) and chronic esophagitis (6.5 %). Only in 32 cases, however, had any esophageal symptoms been noticed during their lifetime, of which in 71.9 % the symptoms appeared after operation for some other disease and 72 % had had vomiting. Only in one case had the diagnosis of esophagitis been obtained during life. The great majority of cases had serious general infections. Reservation was also made for agonal and post-mortem changes. Syphilis, tuberculosis, actinomycosis or blastomycosis were not found in any of the cases. The esophagitis was in the majority of cases localized to the lower third. Microscopic examination showed healing and proliferation of connective tissue. It was therefore considered reasonable to suppose that a stricture might develop on the site of the esophagitis, if there were sufficient repeated scarring. However, no information was furnished on strictures actually observed.

Åberg accounted in 1945 for a familial incidence of a type of benign esophageal stricture which at the time had been contracted by 10 members of the same family, consisting of 7 males and 3 females. The sole symptom consisted of various degrees of dysphagia and began in middle age. Treatment with spasmolytics gave poor result.

Achenbach, Lynch & Dwight described in 1956 a case of advanced esophageal stricture in a patient with ulcerative esophagitis. The disease first appeared with a number of abscess formations which greatly affected his general condition. Operative intervention brought about immediate improvement of his general health and the course of the disease showed a certain analogy with that of ulcerative colitis.

The following case is not unique, but shows such an advanced, long stricture of unknown origin that it may serve as a reminder of the existence of this disease.

CASE REPORT

Our case (N. V. N. 12.08.17) is a 46-year-old turner. He contracted scarlatina in 1937 but had otherwise always been healthy and had never before been to a physician. After a short period of slight epigastrial distress he was admitted to hospital on 9 April, 1958, because of profuse haematemesis. In direct connection with this, increasing difficulties in swallowing were first experienced and six weeks later he was unable to swallow either solid or liquid matter. Simultaneously the sedimentation rate rose from 3 to 50 mm/1 h. X-ray examination and repeated esophagoscopies showed a long stricture from the jugulum height (22 cm from the teeth row to cardia). The process rapidly developed so that only a thread-like passage remained of the lumen. A gastric fistula was applied. Severe cramp pains occurred retrosternally and in the epigast-

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Sliding Esophageal Hiatal Hernia

With a Follow-up Study

BENGT WERNER and THURE WIKLUND

In recent years interest in sliding hernias in the esophageal hiatus has increased considerably. The reason for this is above all that it has been possible to establish the fact that these hernias are often complicated by esophagitis, and that this esophagitis gives rise to a number of symptoms that had previously been explained as of nervous origin.

In the present paper we wish to give an account of our experience from 50 operated, uncomplicated sliding hernias in the esophageal hiatus. Both transthoracic and transabdominal operations are comprised in the material, but we have excluded the few cases we have had in which the patient has been suffering from a very severe esophagitis with shrivelling and shortening of the esophagus, as these cases give rise to quite other problems from the surgical viewpoint.

ANATOMY

The esophageal hiatus may be regarded as a slit in the right crus of the diaphragm. The diaphragmatic musculature constitutes, as it were, a loop around the lowermost part of the esophagus. The vertex of the loop lies forward to the left, while branches run backwards and downwards to the right to their attachment to the uppermost lumbar vertebrae. In this way there is produced a certain angulation between the esophagus and the stomach (Fig. 1). At the vertex of the loop the esophagus is in intimate contact with the diaphragmatic musculature; but just behind the esophagus—before the conjunction of the two branches—there is a small triangular

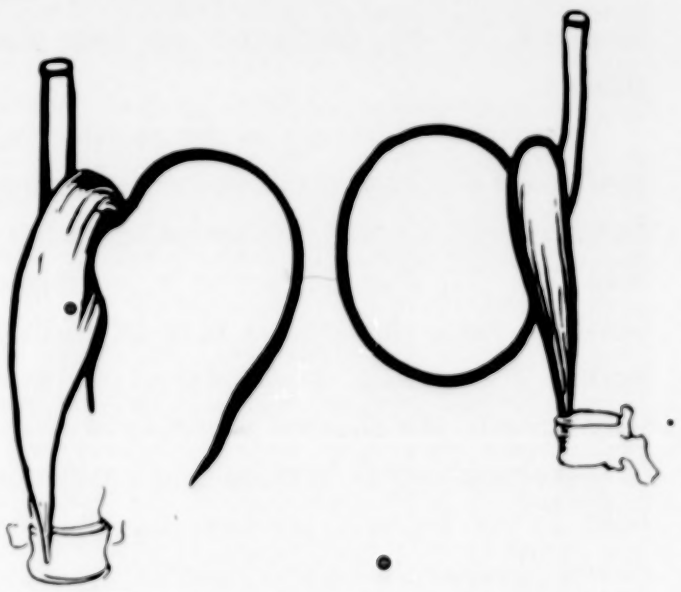


FIG. 1. The right crus of the diaphragm forming a loop round the lowest part of the esophagus. Figure from in front and from the side. (All schematic drawings are taken from Allison, 1951.)

necessitating intrapleural drainage for some days. Seven weeks after the operation the patient was discharged home without any swallowing complaints. A couple of months later he returned requiring a week's drainage of a residual pleural cavity. He was esophagoscoped and the minimal stenosis found in the site of the anastomosis was easily dilated. He has remained free of swallowing complaints.

DISCUSSION

During the course of the disease we could exclude a number of conceivable etiological factors with the help of a careful and complete history and numerous examinations. There was no evidence of tumour or specific inflammation. Heredity and corrosive factors were excluded. There was also no cardinal symptom of reflux esophagitis or peptic ulcer. The general examination did not reveal disease in any other organ, nor any general debility that may result from diseases such as ulcerative colitis. The patient denied abusing alcohol. The chemical analyses of blood and urine were normal.

Since we have eliminated all known etiological factors, we have placed this case in the group of unknown origin. The most remarkable fact, however, in this case was the length of the stricture and the stricture's rapid development after its sudden appearance.

Surgery was resorted to because of the numerous failures in dilating the stricture. The remaining esophageal section then appeared to be sound. It still remains to be seen whether the disease has been arrested or if it will involve the remaining part of the esophagus.

SUMMARY

A report is given of a case of benign, advanced esophageal stricture of unknown etiology. The stricture rapidly resulted in difficulty in swallowing, which could not be improved by dilatations. Surgery yielded good result.

A brief summary of the literature is also presented.

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in the form of a sliding hernia. The phrenoesophageal ligament can no longer withstand the strain, but is stretched to the point at which it allows a greater or lesser part of the stomach to be pushed up into the thorax. That the increased intra-abdominal pressure is of great importance is shown by, *inter alia*, the fact that minor hiatus hernias are very common among pregnant women and that the hernias often disappear after delivery. Hiatus hernias are particularly common among multiparae.

PATHOPHYSIOLOGY

In normal conditions the cardia function constitutes an absolute hindrance to the regurgitation of the acid content in the stomach into the esophagus. There are above all three cardia functions that are considered to be of importance in this connection. (1) The cardia sphincter: That an actual anatomical sphincter exists is doubted by most anatomists; but even if there is no actual sphincter there does seem to be a functional sphincter. (2) Through the oblique outlet of the esophagus into the stomach is formed, as it were, a valve mechanism that may be conceived to function when the pressure in the stomach increases. (3) The angulation of the esophagus at its entry in the stomach through crus diaphragmatica is considered by many writers to be the most important factor as regards the cardia function.

There has been much discussion as to which of these three factors is the most important. In recent years the angulation effect of crus diaphragmatica has been considered by the majority of writers to be of predominant importance. Certain authors are of the opinion that the cardia function is not affected by the elimination of one of the factors mentioned, but that cardia insufficiency would result from the absence of two of the factors. In sliding hernia in the esophageal hiatus the angulation conditioned by crus is lost and there is, furthermore, no longer any oblique outlet of the esophagus into the stomach, the angle between the two having disappeared. One might then expect that in consequence of sliding hernia the cardia function would be insufficient, and would allow the stomach content to pass up into the esophagus. This, however, is not always the case, for there are frequently no signs of the regurgitation of stomach content into the esophagus. This would seem to support the assumption that the functional cardia sphincter, which undeniably exists, plays an important role. Further support for this assumption is provided by the experimental investigations on dogs, in which in different series the different factors for the cardia function are eliminated and in which it has been found that the functional cardia sphincter is alone of importance in this respect. It was possible to move the stomach up into the thorax and allow the esophagus to open into the stomach without any angulation, but the cardia function still remained sufficient. However, one is not justified in assuming that experience from dogs is also applicable to man, for one thing, on account of the different body-positions characterizing dogs and human beings, a factor which may be of great importance in this respect.

Summarizing, it may be said that we



FIG. 2. Sliding hernia in esophageal hiatus. The hernial sac is formed by two layers: the outermost the phrenoesophageal membrane and the innermost the peritoneum. Cardia and the stomach displaced up in the mediastinum.



FIG. 3. Para-esophageal hernia. The hernial sac, consisting of the phrenoesophageal membrane and the peritoneum, is located in front of the esophagus. Cardia located below the diaphragm.

region in which this intimate contact between the esophagus and the musculature of the diaphragm is absent. This region is a *locus minoris resistentiae*, which, in connection with increased intraabdominal pressure, may yield and permit the abdominal organs, especially the stomach, to be displaced up into the thorax.

Two types of hernia in the esophageal hiatus are distinguished: so-called sliding hernias (Fig. 2) and paraesophageal hernias (Fig. 3). The difference in principle between these hernias is that in sliding hernia the cardia is displaced a little way up into the thorax, whereas in cases of paraesophageal hernias the cardia is held in its normal position by the so-called phrenoesophageal ligament (a continuation of the fascia on the underside of the diaphragm) and in some cases by a narrow strip of crus diaphragmatica. These hernias, however, are not only anatomically distinguishable; they also differ, which is more important, pathophysiologically. In paraesophageal hernias the cardia as a rule functions quite normally, i.e. there is no regurgitation of the contents of the stomach into the esophagus, whereas in sliding hernias the cardia function may be insufficient.

ETIOLOGY

The etiology of sliding hernia is considered to be that the esophageal hiatus is wider than normal in consequence of the fact that the branches of the right crus behind the esophagus only contact each other some distance to the rear. The organ which in the first place is pushed up into the thoracic cavity because the pressure in the abdomen is as a rule higher than that in the thorax is the stomach. This displacement of the stomach into the thorax generally occurs

the abovementioned 25 % one must conclude that in 40 % of cases with hiatal hernia one would find some other disease which can explain the symptoms than the hernia.

DIAGNOSIS

Roentgenologic examination of the stomach is the most important method for arriving at the diagnosis of sliding hernia in the esophageal hiatus (Fig. 4). The examination should be carried out with the patient prone and in the Trendelenburg position, as this affords the best possibilities of pressing up a reduced stomach and at the same time of assessing the degree of reflux. It is by no means uncommon for the hernia to be so mobile that it does not appear in the standing or horizontal positions and may then easily be overlooked. The examination should also include a roentgenogram of the esophagus in order to exclude strictures, ulcerations or tumours. One ought further to make it a rule at the same time to make a roentgen examination of the gall-bladder of these patients. From the point of view of differential diagnosis special attention should be drawn to the fact that hiatal hernia may from a roentgenologic examination of the chest be wrongly diagnosed as mediastinal tumour, pulmonary cyst or abscess.

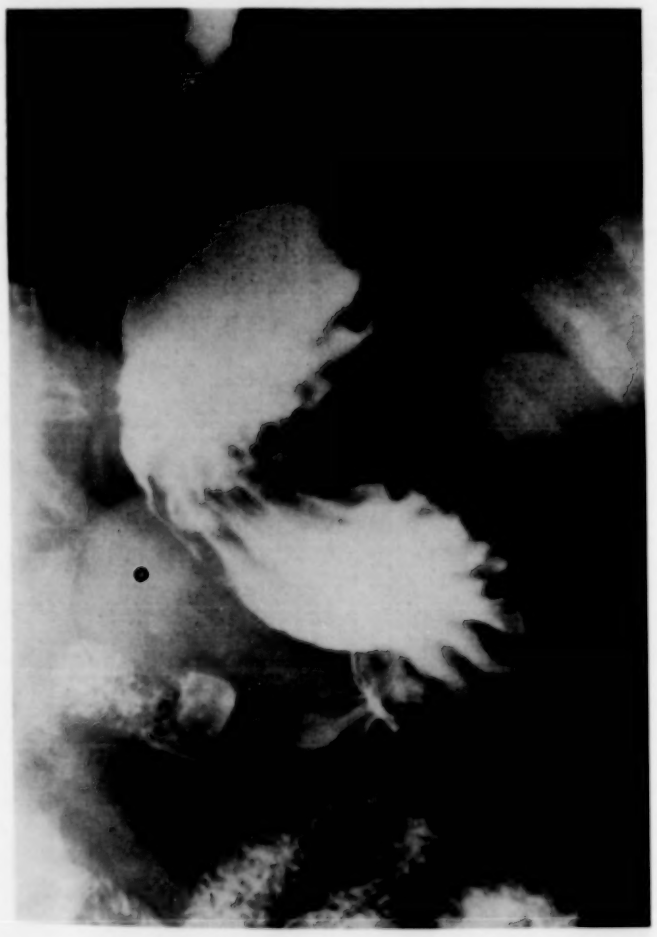


FIG. 4. Roentgen picture of a sliding hernia showing about $\frac{1}{3}$ of the stomach above the diaphragm.

A valuable supplement to the roentgen examination is esophagoscopy. This examination, however, may be reserved only for patients with an obvious dysphagia and in whom the roentgenogram of the esophagus has shown changes requiring more careful elucidation and possibly a biopsy.

INDICATIONS FOR OPERATION

The treatment of hiatal hernia may be either internal medical or surgical. The conservative treatment is only symptomatic. With operation one can restore normal conditions. In order to be able to state the indications for operation confidently, it is important to know the future prospects for patients who are not operated upon. Experience here is not unanimous; but it is obvious that the risk of future complications is not slight (Buchanan, Bowers & Sullivan, 1957). If the patient develops an esophagitis — concerning whose frequency in cases of sliding hernia varying data exist — severe complications with bleeding and esophageal strictures may arise. To this

do not definitely know which factor or factors may be most important for the retention of a normal cardia function, and consequently we do not know either why patients with sliding hernias sometimes develop esophagitis and sometimes not.

INCIDENCE

Minor sliding hernias in the esophageal hiatus are rather common. In 1935 Rigler & Eneboe found that 18 % of pregnant multiparae had such hernias, but that after delivery the hernia disappeared in two-thirds of these cases. In the majority of published materials the females are predominant, but there have also been materials in which males predominated (e.g. Brick, 1949). Fat persons seem to get these hernias more frequently. Most of the patients are over 50 years of age.

SYMPTOMATOLOGY

To put the diagnosis of hiatal hernia on the basis of subjective symptoms alone is difficult, as the symptoms vary and frequently resemble those of other abdominal or thoracic affections.

In hiatal hernia the dominating symptoms derive firstly from the presence of the stomach in the thoracic cavity, and secondly from the dysfunction in the cardia region causing a reflux of the stomach content to the esophagus. The bulging of the stomach sac in the mediastinum gives rise to epigastric or substernal pains after meals and to a feeling of tension or pressure. Nausea, vomiting and intermittent dysphagia are common symptoms. Shortness of breath and precordial trouble sometimes occur together with radiation to the left shoulder and arm, which may lead to an erroneous diagnosis of angina pectoris. The reflux of acid gastric juice to the esophagus causes a discomfort described as heartburn and acid regurgitation. A typical feature is that the horizontal position provokes reflux, and these patients accordingly feel acute discomfort when they bend forward and discomfort at night that may force them to sleep in a half-sitting position. A less common but serious symptom is hematemesis, where the bleeding may derive from the inflamed part of the esophageal mucous membrane or from the herniated part of the stomach.

It is obvious that in many cases hiatal hernia exists without the patient experiencing any subjective symptoms (Brick & Amory, 1950). In other cases it may be difficult to decide whether the hernia is of any importance for the symptoms because in patients with hiatal hernia one often finds other diseases, e.g. ulcer and gallstone, which may give rise to the same trouble as the hiatal hernia. In Brick's material from 1949 including 108 patients with hiatal hernia, other diseases which might explain the symptoms were found in 25 % of the cases; these were, as a rule, duodenal ulcers. Esophagitis was found in only 1 % of the cases. The bile ducts or the gallbladder of these patients were not examined. From other investigations (Wilkinson, 1934; Polley, 1941; Jones, 1941) it is known, however, that among patients with sliding hernia one finds gallstones in about 15 %. If one adds this 15 % to

the following procedure. An incision is made along the median line from the ensiform process to the umbilicus. In order to more easily be able to explore the esophageal hiatus, the suspensory ligament of the left lobe of the liver is divided and the lobe held to the right with a hook. The hernia is reduced by applying traction to the stomach, after which the peritoneum and the phrenoesophageal ligament are incised. The stomach is held to the left with a hook. The right crus of the diaphragm, which forms the esophageal hiatus, is dissected free and the two branches are adapted to each other behind the esophagus with a few No. 000 silk sutures, which are tied very loosely, so that the adaptation is done without damaging the muscle fibres. The esophageal hiatus is closed so as to allow only the passage of the esophagus and the tip of the forefinger. The incised edges of the peritoneum and the phrenoesophageal ligament are then sutured to the under surface of the diaphragm together with a few sutures between the diaphragm and the esophagus.

CLINICAL EXPERIENCE

Material

The clinical material represents our experience from the surgical treatment of 50 patients with sliding hernia in the esophageal hiatus from 1932 up to and including November, 1958, at Sabbatsbergs sjukhus, Stockholm.

Sex and age

Of the 50 patients operated on for sliding hernia, 37 were women and 13 men. The oldest patient was 78 years of age and the youngest 10 years; the average age was 54 years. The hernias were commonest in the age-group 50–70 years.

Operative methods

During the 17-year period covered by the follow-up study a varying technique for the repair of hiatal hernias has been applied, as regards both the transthoracic and the transabdominal operations. Formerly we most frequently operated transthoracically, but in recent years we have for the most part operated trans-

TABLE 1. Survey of fifty operated sliding hernias in hiatus esophagi.

Operation	No.	Reduced in standing pos. (roentgen)	Not reduced in standing pos. (roentgen)	Patients with cholelithiasis	Patients with gastric ulcer, duodenal ulcer	Number of followed-up cases	Recurrences
Thoracic operation		1	17	—	3		
Op. acc. to Allison	5					5	—
"Atypical operation"	13					10	1
Abdominal operation		13	19	15	5		
Op. acc. to Allison	20					19	—
"Atypical operation"	12					11	3
Total	50	14	36	15	8	45	4

must be added the risk of strangulation of the hernia. In some cases with large sliding hernias we have seen very large gastric ulcers appearing precisely in that part of the stomach adjacent to the widened esophageal hiatus.

In our opinion there are absolute indications for operation in cases showing symptoms of esophagitis and in all cases with large hernias, as experience shows that these hernias may produce pressure on the adjacent thoracic organs and are, furthermore, more exposed to the risk of strangulation. By large hernias we mean those in which $\frac{1}{3}$ of the stomach or more is above the diaphragm. Relative indications for operation exist in those cases in which the genesis of the patient's abdominal trouble is not clear, but where the diaphragmatic hernia may be provoking the symptoms. We also consider it to be indicated that in patients undergoing operation for ulcer or cholelithiasis an existing hiatal hernia should be repaired at the same time, as this may very well have given rise to a number of the symptoms.

OPERATIVE METHOD

The method for the operation of sliding hernia has varied in the course of the years as regards both closure technique and the line of attack via the thorax or abdomen. Since the rapid development of thoracic surgery in the 1940's, the transthoracic operations have been predominant, and with the operative methods devised by Sweet (1948 and 1952), Allison (1951) and Husfeldt (1952) such entirely satisfactory results have been attained that the technique itself does not at present constitute any major problem.

During the last few years we have at the Sabbatsbergs sjukhus operated according to the principles designed by Allison, as we consider that this not only takes into account a good anatomical result, but also ensures that the function in the cardia region shall be restored to normal conditions.

Allison operates on his patients transthoracically, but he is of the opinion that the enlarged hiatus may just as well be closed transabdominally according to the same principles. Several writers draw attention to the advantages of the transabdominal operation and have not in this connection found any increased frequency of recurrence (Harrington, 1955; Beardsley, 1956; Beretta & Jordan, 1957; Carver, 1958). One of the most important advantages is that one can at the same time carry out a complete abdominal exploration. Although the occurrence of other intra-abdominal pathological states can, as a rule, be established preoperatively, it is nevertheless in certain cases not possible, with current methods of examination, to reveal their existence. It should also be taken into account that the hernias are not located in the pleural cavity but within the posterior mediastinum. Owing to the possibility of pleural complications, it is not advisable to open the pleural cavity when an operation from the abdomen admits of a satisfactory repair. Moreover, an operation from the thorax in many cases more or less impairs the lung function through adhesions between the pleural surfaces.

During the last few years we have used

similarly, a patient with hiatal hernia should always have a roentgen examination of the gall-bladder. In our material 14 cholecystectomies and 1 cholecystolithotomy were performed. In all the cases with gastric ulcer we restricted ourselves to an excision of the ulcerous region, an operative method that otherwise gives poor results with ulcers; but in cases like these, where the hiatal hernia probably played an essential role in the origin of the ulcer, it should be sufficient, as at the same time the hiatal hernia was radically operated on. In all cases the ulcer was located in that part of the stomach which through pressure against the esophageal hiatus was possibly exposed to disturbance of the circulation. Both the duodenal ulcers were treated with gastric resection ad modum Billroth II. Three of the gastric ulcers are included in the group operated upon transthoracically.

Complications

Owing to the close contact between the spleen and the upper part of the stomach, it is understandable that one of the commonest complications in the repair of hiatal hernia should be damage to the spleen. In 6 cases the spleen capsule was ruptured, and the ensuing bleeding was so severe in 5 cases that the spleen had to be extirpated, while in one case it was possible to stop the bleeding with capsular suture.

More serious postoperative complications which were a direct consequence of the operation for hiatal hernia occurred in three cases. These were empyema, mediastinitis and ileus of the small intestine.

Results of the surgical treatment

Assessment of the results of the surgical treatment was based on a follow-up study of 45 patients. Five patients had died before the follow-up study was carried out. One patient aged 78 years who was operated upon transthoracically died 1 month after the operation from cardiac incompensation. A further 4 patients died a long time afterwards without any connection with the operation. In all cases the follow-up study consisted of roentgenologic examination of the stomach and an analysis of any subjective symptoms.

In 4 of the 45 patients the hernia recurred. In all 4 cases the operative method applied had in essential points deviated from that described by Allison. Three of these cases had been operated upon transabdominally and 1 from the thorax. In two of these cases the remanent symptoms were so severe and the hernia of such an order of magnitude that reoperation was necessary. After this there was no recurrence. In the two remaining cases there was major hernial recurrence, but the patients had no symptoms, so no further operative measures were undertaken. The majority of the remaining 41 patients without recurrence were free of subjective symptoms. Although the roentgenologic examination had not revealed any recurrence, 14 patients had more or less persistent symptoms which on the whole agreed with those occurring before the operation In no case did the roentgenologic examination reveal any gastric ulcer.

abdominally. Eighteen patients have been operated on from the the thorax and 32 patients from the abdomen. Since, as already mentioned, we have drawn attention to the advantages of Allison's operative method as regards both the anatomical and the functional result, we have for the last few years consistently applied this method, though with the modification that the operation has been performed transabdominally. For the sake of comparison the transthoracically and the transabdominally operated patients have been divided into two groups: those operated upon with Allison's method and a miscellaneous group in which varying techniques have been applied, the latter under the heading "Atypical operation" in the table (see Table 1).

Reducible and irreducible hernias

In many cases sliding hernias are reduced when the patient stands up, but in other cases the hernia remains in the thorax, even when the patient is standing. Many writers have considered that in these last-mentioned cases the esophagus is shortened, and in this way holds the hernia above the diaphragm. This has been taken as an argument in favour of operating on such hernias with thoracotomy, as this would afford a clearer survey of the conditions obtaining. Experience shows, however, that a really short esophagus is very uncommon in cases of hiatal hernia and occurs, practically speaking, only in cases with severe esophagitis, in which shrinking and shortening of the lower part of the esophagus have taken place. If there is no pronounced esophagitis, then one may count on the esophagus being of normal length. In our series the hernia was irreducible in the standing position in 36 cases. Nineteen of these were operated upon with laparotomy, and in no case was any difficulty experienced in pulling the hernia below the diaphragm, even if the hernia comprised practically the entire stomach.

An hiatal hernia that is irreducible in the standing position does not constitute an indication for thoracotomy except in cases in which there is severe esophagitis with shrinking of the lower part of the esophagus. These last-mentioned cases constitute a special surgical problem which falls outside the scope of this paper.

Associated diseases

In 23 of the 50 cases it was necessary to undertake other operative measures at the same time as the hernia was operated upon. It is very interesting to observe that 15 patients were at the same time operated on for cholelithiasis, 6 patients for gastric ulcer, 2 for duodenal ulcer and one for ovarian cyst. One of the cases was operated upon simultaneously for both cholelithiasis and gastric ulcer. Furthermore, 7 patients had been previously operated upon for cholelithiasis. Some of these last-mentioned cases had a continuation of symptoms, and it is possible that even at that time they had an undiagnosed hiatal hernia. For this reason, in the case of a cholelithiasis patient who does not manifest clearly characteristic symptoms, one should always take a roentgenogram of the stomach with special attention to the possible occurrence of hiatal hernia; and

was possible (5 patients had died before the follow-up study was carried out). Among these 45 there were 4 recurrences, thus approx. 10 %. There were no recurrences in the group operated upon according to Allison.

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CONCLUSIONS AND SUMMARY

Sliding hiatal hernia is a not uncommon complaint frequently giving uncharacteristic symptoms which may simulate all kinds of abdominal and thoracic diseases, e.g. ulcer, cholelithiasis and angina pectoris. Undoubtedly sliding hernia can sometimes be entirely asymptomatic. One often finds these hernias simultaneously with other diseases in the upper part of the abdomen, so that in the actual case it may be difficult to decide upon the source of the patient's symptoms. In some cases the cardia function is disturbed, resulting in esophagitis. In cases of esophagitis there is the threat of complications in the form of bleedings and stricturing of the lower end of the esophagus. Major hernias encroach upon the space of the thoracic organs and risk becoming incarcerated. All major hernias and all hernias with esophagitis should be operated on; and the authors are also of the opinion that any sliding hernia should be repaired in patients who are undergoing operation for cholelithiasis or ulcer, even if the hernia is small and there is no esophagitis.

Previously these hernias were operated upon in all sorts of ways. The enlarged hiatus, for example, was closed by suturing both in front and behind the esophagus; a number of surgeons incised the diaphragm from the esophageal hiatus up towards the dome of the diaphragm and shifted the hiatus up towards the top of the dome. These and similar operations were connected with a high frequency of recurrence, e.g. Husfeldt (1952) and Stensrud (1954). With the operative methods described by Allison (1951) and Husfeldt (1952) the frequency of recidivation has been much reduced, e.g. Stensrud (1954) and others, who have operated according to Allison, and Malm (1958), who has operated according to Husfeldt. We consider the operative method described by Allison to be the best.

In recent years there has been much discussion as to whether thoracotomy or laparotomy should be adopted in these cases. The authors are of the opinion that the abdominal approach is the most suitable. We think this is motivated above all by three considerations: (1) If one operates from the abdomen, one can at the same time make a thorough exploration of the abdomen, which is of the greatest value, since in many cases one does not know whether the symptoms derive from the hernia or from some abdominal affection. (2) Any operation for cholelithiasis, ulcer or other abdominal disease that may be called for can be undertaken at the same time. (3) After every thoracotomy one runs the risk of a certain impairment of the lung function. As in these cases one has generally to do with somewhat older and fat persons, it is of particular importance to avoid interfering wth the lung function. The opponents of the transabdominal operation are of the opinion that it is easier and safer to perform the operation from the thorax. We have had experience of both methods, and we are convinced that the abdominal approach affords at least as good a survey of the operative field and equally good opportunities of operating according to Allison's principle.

The authors' material consists of 50 cases, in 45 of which a follow-up study

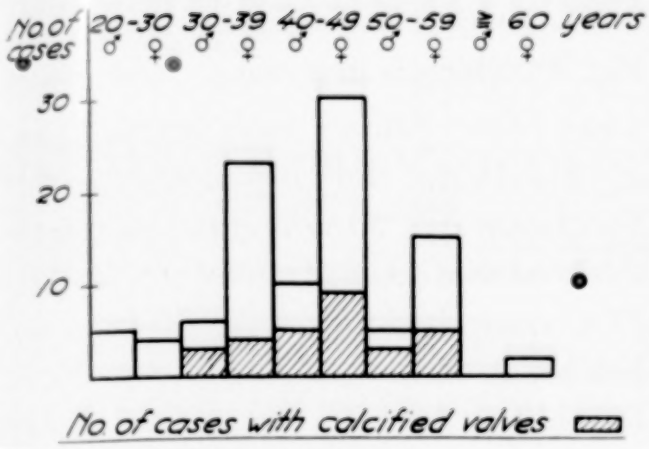


FIG. 1. Age and sex distribution.

calcification, and on re-operation it was obvious that the return of symptoms had been caused by continued accretions of calcium while the commissures were still open. In a further two cases where exploration revealed a virtually pure insufficiency, the valves were likewise left intact. In all the other cases, with pure or predominant stenosis, commissurotomy was carried out either digitally or instrumentally.

Two patients died in connection with the operation. One of them (case 47, A. H.) had as well as valvular calcifications, an adhesive pericarditis with deposits of calcium, and died 19 days after the operation from combined circulatory, respiratory and renal insufficiency. The other (case 60, E. K.) had also valvular calcifications and considerable insufficiency in the mitral ostium, as well as an associated lesion of the aortic valves. This patient died in heart failure on the third post-operative day. Neither of these patients was found at operation to have any thrombus in the atrium, and there were no signs of calcium embolism.

The distribution of the material with reference to age and sex is shown in Fig. 1. All patients belonged to the functional groups II–IV, the majority being in group III, and all but one had undergone cardiac catheterization before the operation.

Varying degrees of calcification of the mitral valve were observed at operation in 29 of the patients (approx. 30 %) and occurred in all ages except in the group under 30 years (see Fig. 1). Half the men over 30 years had calcium in their valves as against $\frac{1}{4}$ of the women. Valvular calcification occurred in association with both sinus rhythm and atrial fibrillation, but was commoner among patients with fibrillation. It was also encountered more frequently in cases with pronounced enlargement of the heart than in those with moderate enlargement (see Fig. 2). Attempts to determine the presence of calcification preoperatively by screening were not made consistently except in the latter half of the series. In only 11 cases out of 18 with valvular calcification seen at operation had this been previously shown by fluoroscopy. With improved technique, however, it should

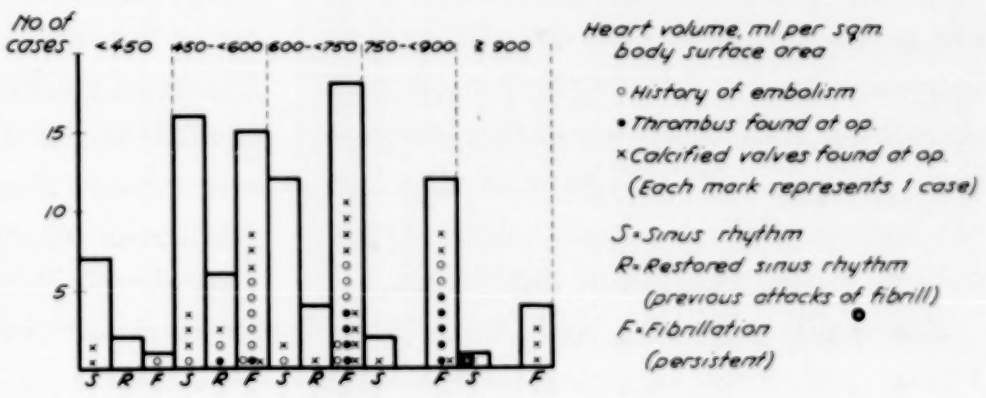


FIG. 2. History of embolism and presence of thrombi and calcified valves in relation to heart size and rhythm at the time of operation.

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Thrombo-embolic Complications in Mitral Commissurotomy

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The occurrence of fresh thrombi in the left atrium in cases of mitral stenosis constitutes a serious complication from the point of view of heart surgery. During the operation such thrombi may become detached and give rise to embolism, perhaps so severe as to threaten the life of the patient. In pre-operative care therefore, as in conservative treatment, one must try to preclude the formation of intracardiac thrombosis or to accelerate the organization of already existing thrombi, and prevent further agglutination of these.

Favourable experience with such prophylaxis in patients with recurrent embolism has been reported by e.g. Cosgriff (1953) and Carter, McDevitt, Gatje & Wright (1958) who found the incidence of recurrence considerably reduced during treatment with dicumarol. There were, however, no operated patients included in their series.

Another important complication in the operation for mitral stenosis is calcification of the valves. Where this is extensive, it is our experience that the prospects of a functionally good result are greatly reduced. The demonstration of such calcifications by means of fluoroscopy is therefore important for assessment of the prognosis. The immediate risk with calcified valves, however, is the fact that when the valves are dilated fragments of calcium may be torn off and give rise to embolism. There is at present no known medical treatment which can hinder valvular calcification, so the prevention of possible calcium emboli in connection with the operation is purely a problem of surgical technique.

We shall give here an account of our experience of thrombotic and embolic complications in the surgical treatment of mitral stenosis.

MATERIAL

Incidence of valvular calcification and intracardiac thrombosis

The material consists of the first 100 consecutive cases operated upon at the Gothenburg Children's Hospital* during the period March 1952 to February 1959. One of these (case 81, J. U. 070723) had been operated upon seven years previously by Prof. Crafoord with a primarily satisfactory result. On that occasion there was already considerable valvular

* The hospital has for various reasons been the only centre for cardiac surgery in Gothenburg and surrounding parts of Sweden; this applies to adults as well as children.

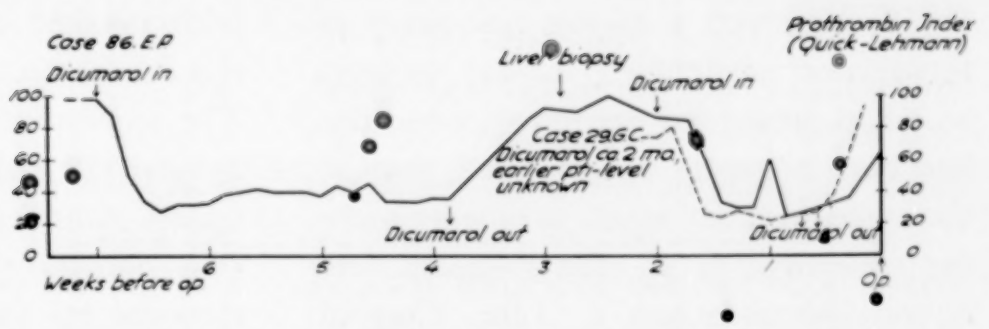


FIG. 3. Prothrombin level in Cases 29 and 86 during preoperative treatment with dicumarol.

had no preoperative dicumarol treatment, 5 had thrombi in the left atrium, seen at operation. Two of these had only a small organized thrombus in the auricle; one had a large disc-shaped thrombus which adhered firmly to the lateral wall of the atrium; one had a couple of small, polypous thrombi; and the fifth had an abundance of fresh thrombi in the atrium.

Of the 35 patients with fibrillation who received dicumarol treatment, 5 again had thrombi in the left atrium. One of these (case 37, B. J.) had in addition to a thrombus in the auricle a polypous thrombus about the size of a digital phalanx just beside the mitral ostium; both of these appeared to be organized. Of the remaining cases, two had, apart from a thrombus in the auricle, a large organized thrombus which in one case (case 30, K. P.) was polypous, and in the other disc-shaped, firm, and adherent to the lateral atrial wall (case 58, R. L.). All these three had had emboli before operation. The other two cases, which had no history of embolism, had more or less fresh thrombi. One of these (case 86, E. P.) had a fresh thrombus, more than thumb-sized, immediately below the very constricted auricular base. In this patient the prothrombin index according to Quick–Lehmann (Lehmann, 1941) was held below 50 for 2–3 weeks, after which the treatment was discontinued on account of a liver biopsy (see Fig. 3). In the other case (case 29, G. C.) operation revealed abundant floating thrombi, partly fresh. The prothrombin index here was at a satisfactory level for a week before operation (see Fig. 3), but had probably been higher previously; there are, however, no data concerning the prothrombin level during the 2–3 months of treatment before admission.

Among the possible causes of failure of dicumarol treatment in the last two cases, the following may be mentioned.

(i) The period of effective treatment may have been too short. Carter *et al.* (1958) were able to show a continued reduction of the incidence of recurrence during dicumarol treatment up to 6 weeks after an embolic episode; beyond this period no further reduction was obtained. This would indicate that treatment with anticoagulants should be given for at least 6 weeks in order to ensure the best possible result. The treatment must also be adequate, i.e. the prothrombin index according to Quick–Lehmann should be between 30 and 50–60 (Lehmann, 1943), corresponding to a P & P concentration according to Owren of between 10 and 30 % (Owren & Aas, 1951).

(ii) The treatment may have been discontinued too abruptly. Carter *et al.*

be possible to obtain a positive roentgen diagnosis in a higher proportion of cases (Bartley, 1958).

Sixteen of the patients had had clinically diagnosed embolism (e.g. brain, legs) 1 month to 8 years before the operation. Three of these had two or more embolic episodes. Multiple embolisms have in untreated material been considered to occur in more than half of all cases of embolism, the majority of recurrences appearing within 6 months after the previous attack (Daley, Mattingly, Holt, Bland & White, 1951; Cosgriff, 1953). As operation was only in exceptional cases performed within such a short period, the relatively low incidence of recurring embolism in our material can therefore possibly be ascribed to treatment with anticoagulants. A further six patients had suspected systemic emboli, which were difficult to diagnose, however, on account of their obscure symptoms, or their localization (e.g. kidneys, mesenterium). The same applies to lung emboli, which occurred in a few cases.

Only in 3 of the 16 patients with previously diagnosed systemic embolism was any thrombus revealed in the left atrium at operation. One cannot, however, exclude the possibility that minimal thrombi may have been overlooked. According to de Otaduy (1956), these are rather common and are difficult to demonstrate. In 3 cases the auricle was shrivelled, indicating an earlier thrombotic process. Of the 84 patients who had not had any definite clinical signs of embolism, 8 had thrombi in the atrium.

Practically all cases with thrombosis and/or embolism (approx. 25 % of the total material) had atrial fibrillation (see Fig. 2), which is in good agreement with what other authors have found. Daley *et al.* (1951), for instance, observed fibrillation in 90 % of their conservatively treated series of embolism, of which 97 % comprised mitral valve lesions; and Belcher & Somerville (1955), who found thrombi in the left atrium in 68 of their 430 operated cases of mitral stenosis, reported fibrillation in all of these. In our series there was about the same percentage of emboli in patients with moderate enlargement of the heart (i.e. heart volume 450–600 ml per sq. meter body surface) as in those with more pronounced enlargement (i.e. heart volume > 600 ml per sq. meter). Intracardiac thrombi, on the other hand, were found chiefly in patients with large hearts (see Fig. 2). The majority of these had no manifest emboli, which can perhaps be related to the impaired circulation in these cases.

PREOPERATIVE DICUMAROL TREATMENT

All patients with a history of clinically established or suspected embolism were given dicumarol, either continuously or at least for several weeks following the embolic episode. Several patients who had not had emboli were also treated prophylactically with dicumarol, sometimes for months, but as a rule only for the few weeks immediately preceding operation. In all, 11 of the 50 patients with sinus rhythm and 35 of the 50 fibrillation cases were treated with anticoagulants. We shall deal here with the findings only in the fibrillation cases.

Of the 15 patients with fibrillation who

fragments have been left to be washed out with the blood stream through the incision.

No thrombus in the auricle has given rise to embolism in connection with the operation.

Disc-shaped thrombi, attached to the atrial wall, were found in two cases (case 10, K. A.; case 58, R. L.). In both cases these thrombi were attached to the inside of the lateral wall of the atrium and extended from the auricle down to the annulus tendinosus. They were oval in shape and 1–2 cm in thickness. They had tapering edges and on the side adjacent to the atrial wall merged directly into the endocardium. The edge of one of these thrombi was submitted for microscopic examination, and showed: "Typical mixed thrombus, partly in process of organization and partly transformed to connective tissue."

These thrombi were in all cases left *in situ* for continued organization, and in no such case was commissurotomy followed by embolism.

Polypous, floating thrombi were observed in five cases. These thrombi also derived from the lateral wall of the atrium. Their size varied: in three cases they were thumb-sized (case 29, G. C.; case 30, K. P.; case 86, E. P.); in a fourth case there were two floating finger-sized thrombi (case 80, E. S.); and in the fifth case the thrombus was no longer or thicker than a digital phalanx (case 37, B. J.).

The surgical technique varied in accordance with the type of thrombus and the degree of its organization. The basic principle has been to leave intact those thrombi which could be presumed to be in process of organization and whose localization did not constitute an obstacle to the performance of commissurotomy. Thrombectomy was performed in two cases. In the one case (case 37, B. J.) a thrombus the size of a fingertip was extracted near the mitral cusps with a specially-constructed thrombus forceps. The operation was performed with temporary bilateral clamping of the carotid arteries according to Bailey (Bailey, Olsen, Keown, Nichols & Jamison, 1952). There was in this case no embolic complication. In the second case (case 80, E. S.) two plumsized thrombi and one smaller thrombus were extracted digitally through the auricular incision. In this case the carotids were not clamped off and embolism ensued in the iliac artery. The offending embolus was palpated just as it vanished through the mitral ostium, and was estimated to be about the size of an almond. This patient also had an embolism in the ophthalmic artery.

As already mentioned, calcifications of the mitral cusps were found in 29 cases. In ten of these they took the form of excrescences which could easily be torn off in the course of commissurotomy, and give rise to embolism. To preclude this possibility, a temporary, bilateral clamping-off of the carotids according to Bailey was resorted to in the majority of cases. For technical reasons in one case (case 77, B. L.) only the left carotid was clamped off, and a right-sided cerebral embolism occurred. In two other cases there were cerebral complications despite temporary clamping of the carotids (case 33, L. J.; case 64, F. A.). In one case it was possible to get hold of a

(1958) observed a higher frequency of recurrence particularly among patients who had prolonged treatment, when this had been abruptly discontinued, than in the same patients when they were without treatment at all (the so-called "rebound phenomenon"). Like Cosgriff (1953) they therefore recommend gradual diminution of the dose before treatment is entirely discontinued. According to Carter *et al.*, however, the increased risk of recurrence is not so much in evidence during the first week after the discontinuation of the treatment as during the subsequent 5–6 weeks.

From this investigation it emerges (*a*) that complete organization of intracardiac thrombi may occur without anticoagulant treatment, and (*b*) that fresh thrombi may be found at operation despite such treatment, though it is conceivable that the treatment was not continued long enough or had in some other manner fallen short of the ideal. In such a limited series, and with a lack of uniformity in treatment, it has unfortunately not been possible to show whether preoperative treatment with anticoagulants reduces the incidence of intracardiac thrombi, and with it the risk of embolism in connection with operation.

The favourable effect of dicumarol treatment in cases of recurring embolism, which has been reported from several quarters, supports, however, the inclusion of such prophylaxis in the preoperative treatment of mitral stenosis. Our own experience and that of others seems to indicate that this prophylaxis should not be restricted to cases with a history of embolism, but that other patients with atrial fibrillation, and at least those with marked enlargement of the heart, should be treated with anticoagulants. The indications must here be weighed against the risks and the practical difficulties connected with such treatment. It is possible that the demonstration of thrombi in the left atrium by angiocardiography may be a valuable aid in the weighing of pros and cons. We have no experience of this method of examination, however, in cases of mitral stenosis.

SURGICAL VIEWPOINTS

Three different types of thrombi were observed in this series: (1) Small auricular thrombi; (2) large disc-shaped thrombi attached to the atrial wall; (3) large polypous thrombi.

Small auricular thrombi were seen in nine cases. In two cases they had direct continuity with thrombi attached to the atrial wall. In three cases they were associated with polypous thrombi in the atrium. Organization of a thrombus in the auricle is followed by shrinking of the latter; in seven cases such shrinking was noted indicating earlier thrombosis. In two of these cases the shrunken auricle was associated with polypous thrombi.

In cases where a thrombus was palpated in the auricle on exposure of the heart, we first tried to ascertain whether it was isolated or whether it had continuity with a thrombus fixed to the atrial wall. In the former case, the base of the auricle was clamped off, after which the auricle was opened and evacuated. In the latter case, the heart was opened without previous clamping-off and as much thrombus extirpated as was necessary to give access to the auricle. The thrombus

15 seconds' bilateral clamping of the carotids during the commissurotomy. This patient also showed post-operative coma (like protracted narcotic sleep) for 4 hours, without signs of shock. Tracheotomy was performed because of stagnation of mucus in the respiratory passages. However, the patient woke up relatively quickly without any definite neurological symptoms, and after a further 6 hours she appeared clinically normal. The third case with advanced calcifications of the mitral cusps but no atrial thrombus (case 64, F. A.) had the carotids clamped briefly during the commissurotomy. This patient awoke quite normally after the anaesthetic, but some hours later he complained of flickering vision in the left eye. An ophthalmic examination showed partial limitation of the field of vision in this eye following embolism in the central artery of the retina.

The fourth case (case 80, E. S.) had thrombi in the left atrium but no valvular calcifications. In this case the carotids were not clamped off during commissurotomy. The patient awoke normally from the anaesthetic, but the same day she showed signs of a left-sided hemianopia indicating damage to the optic tract possibly caused by an embolism in the striate area. In the same patient, there were signs of embolism in the right external iliac artery. After 24 hours there was a maximal difference in temperature between the two legs at knee level of 3.8°C. The circulation and even the mobility in the right leg was, however, so satisfactory all the time that embolectomy did not seem indicated. All the symptoms abated in the course of the next two weeks.

These four cases with primary embolism complicating operation illustrate the importance of surgical prophylaxis by clamping the carotids during the intracardiac manipulation. This applies not only to cases with atrial thrombi, but also those with calcification of the mitral valves. Cases 33 and 64 both show the risk of making this clamping off too brief. There is evidently no guarantee that a detached embolus will follow the most rapid central blood stream, and one must reckon with an occasional "delayed" embolism.

This series also includes two cases with secondary thrombosis and embolism The first patient (case 47, A. H.) had a stormy post-operative course but no primary signs of embolism. On the 16th day he showed signs of thrombosis in both right arm and right leg. Heparin and dicumarol were administered, but two days later, when the prothrombin index was 47, the patient got an embolus in the left popliteal artery. The following day the patient died of acute anuria with steeply rising serum potassium. The second case (case 86, E. P.) had thrombi in the left atrium at operation, which was completed without clamping off the carotids. There was atrial fibrillation before and after operation. The post-operative course was completely normal until the 4th day, when signs of right-sided cerebral embolism with facial paresis were observed. These signs disappeared after 6–7 hours, and the further post-operative course was uneventful.

As regards secondary thrombosis and embolism, it is interesting to note that only one patient (case 47, A. H.—see above) showed clear signs of venous

small fragment of calcium with the finger and remove it from the atrium.

In all operations, and especially in blind operations, it is of great importance to be well oriented in the operative field. In blind operations in the left heart a careful palpation of the atrium is necessary. In all our cases palpation was done with the bare finger. This permits a more precise and less traumatic palpation of possible thrombi, and a better assessment of their degree of organization. It is likewise of great importance to make a careful palpation of valvular calcifications before commissurotomy is undertaken. In cases in which there is risk of embolism, the carotid arteries should be temporarily clamped bilaterally, as recommended by Bailey. This certainly precludes the possibility of major embolism in the carotids, but, as emerges from this material, it is no guarantee against small emboli in the fine cerebral arteries.

IMMEDIATE POSTOPERATIVE CARE

The possibility of silent embolism in connection with operation cannot be excluded. In the present series routine examinations in an attempt to discover such emboli were not undertaken. Theoretically, a minor cerebral embolism might be hard to differentiate, clinically, from a situation due to a brief general cerebral hypoxia (in cases of temporary massive blood loss or heart failure from other causes during the operation, or following the bilateral clamping-off of the carotids for short periods). An analysis of the individual cases in this series, however, renders it unlikely that such confusion has occurred. In no case where embolism has been diagnosed postoperatively has there been any episode during the operation in which cerebral hypoxia might have arisen. In the case with the most protracted bilateral carotid clamping (70 + 90 + 15 + 15 seconds with at least 2 minutes' free carotid flow between clamped periods) there were no clinical signs of embolism; and neither in this nor in any other case with carotid clamping have we found any ensuing signs of cerebral hypoxia.

During the period immediately following the operation 6 patients developed signs of thrombo-embolic complications. In 4 of these, the signs were evident immediately after operation, so that the only possible interpretation is that they were caused by mechanically detached emboli at operation.

In three of these cases no atrial thrombi had been definitely seen, but there were rough calcifications on the mitral cusps. In one of them (case 6, B. L.), on account of technical difficulties, only the left carotid artery had been clamped off during commissurotomy. This patient lay comatose, but without signs of shock, for 10 hours after operation, and on awakening had a left-sided hemiparesis. On account of pharyngeal paresis and to avoid aspiration of gastric contents, tracheotomy had to be performed. He was mentally confused for 3 days. After 14 days, the tracheal cannula could be removed and from the 19th day the patient had so improved as to be able to go for short walks. There was no significant mental change. Another case with calcified valves but without atrial thrombi (case 33, L. J.) had only

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The Postcommissurotomy Syndrome after Mitral Valvotomy

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The postcommissurotomy syndrome (PCS) was first described by Soloff, Zatuchni, Janton, O'Neill & Glover (1953) as a condition with pains retrosternally and in the left half of the thorax in combination with a moderate rise in temperature, which symptoms made their first appearance quite suddenly one or a few weeks after valvulotomy. The symptoms remained for 10 days to four weeks.

Similar symptoms after mitral operations have subsequently been described from many different quarters. The symptom complexes vary somewhat, but they represent on the whole an exacerbation or a recidivation of the normal postoperative discomfort with pains in the operated region or in the left shoulder, rise of temperature and in some cases exudate in the pericardiac cavity and/or in the left pleura. The frequency of PCS varies between 10 and 40 % in different materials.

The nature of the changes is not clear. Among suggested explanations are a recurrence of the etiological rheumatic process (Bercu, 1953), "idiopathic pericarditis" (Dressler, 1954), pericarditis + pleuritis released by the operative trauma (Elster, Wood & Seely, 1954) or an effect of oozing from the auricular wound, as shown by the blood-stained effusion, responsible for a recurrent pleuro-pericarditis (Papp & Zion, 1955).

MATERIAL

We give an account here of the occurrence of symptoms resembling PCS among 106 patients operated upon for mitral stenosis at the Sabbatsberg Hospital in Stockholm during the years 1952–1957. The distribution of the sexes is 82 women and 24 men. The age varies between 18 and 63 years, with an average age of 40 years. The postoperative observation period was on an average 64 days. The reasons for this long period were firstly that the clientèle consisted to a large extent of primarily bad cases, and secondly that a considerable group (33 cases) had been given postoperative treatment with cortisone preparations for a long period in order to counteract the suspected risk of secondary shrinking and adhesion of the operated valves with restenosing as a result.

RESULTS

Secondary intensification of the postoperative symptoms occurred in 16 pa-

thrombosis, and this during an extremely complicated post-operative course with respirator treatment, parenteral nutrition, etc. Obviously, in these patients, as in other post-operative cases, early ambulation—the patient preferably getting up within 48–72 hours—is of great importance.

The two cases of secondary arterial embolism observed can hardly be related to the cardiotomies performed.

SUMMARY

The authors report their first 100 consecutive cases of operation for mitral stenosis. Sixteen cases had a history of systemic embolism; and in a further 8 thrombi in the left atrium were found at operation. The total incidence of verified pre-operative thrombo-embolism in this series was thus 24 %. In 29 cases calcified cusps were found at operation.

The possibilities of improved pre-operative diagnosis of valvular calcification and intracardiac thrombosis, the value of prophylactic dicumarol treatment and the surgical technical precautions in connection with commissurotomy are discussed.

The total morbidity as regards thrombotic and/or embolic complications in connection with operation was 6 %, of which 4 % were primary and 2 % secondary complications. The mortality and the post-operative invalidity due to the complications discussed were nil. The total mortality was 2 %.

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with PCS in relation to the rise in temperature.

ECG shows in general pathological S–T and T changes immediately after the mitral operations. These changes are probably in part an expression for traumatization of the pericardium during the surgical operation. In connection with PCS there occurred increased deviations in S–T or T which could not be explained only as frequency effect. In five cases these deviations occurred diffusely over the surface of the heart and in three cases over locally delimited regions. In two cases no increased ECG deviations could be shown.

TABLE 1. Frequency of essential symptoms in ten cases of postcommissurotomy syndrome.

Symptoms	Number
Pains in left shoulder or in operative area	9
Rise in temperature	10
Heightened SR	10
Roentgenological pericardial exudate	3
Roentgenological pleural exudate or increase of existing exudate	5
ECG with increase of previous S–T and T changes	3

Diagnosis

We have tried to rule out other pathological states which might give rise to these symptoms by continuous clinical observation of the patients. Unfortunately the diagnostic work is rendered difficult by the postoperative deviations from normal anatomy and normal physiology which were already present when PCS was first manifested.

In one single case there were simultaneously slight and brief pains in both wrists without concomitant swelling or restriction of movement. Otherwise no signs of joint affections were shown, nor was it possible to show any signs of resurgent rheumatic activity. Nor, furthermore, were there any signs of specific infection of any kind. No virological examinations were carried out.

Clinically, the condition appeared only as an exacerbation of the "normal" postoperative symptoms, and it was not possible to show any releasing etiological factor.

Therapy

Symptomatic treatment, with warmth, analgesics and movements, was started as soon as the pains began to abate. The cases with high fever occasioned the administration of antibiotics or change of antibiotics in those cases in which the postoperative antibiotic therapy was still being applied. The effect of this antibiotic treatment appears very dubious. In a couple of pain-resistant cases roentgen therapy was applied to the shoulder, which possibly accelerated the abatement of the pain. Tapping of large pleural exudates is indicated.

The *prognosis* was good in all cases.

DISCUSSION

It is of a certain interest to try to decide whether these PCS cases represent rheumatic recidivation (Soloff, 1953; Bercu, 1953) or a local state of irritation caused by postoperative oozing from the auricular wound or other mechanically or toxically irritating factors (Elster, Wood & Seely, 1954; Papp & Zion,

tients. In six of these there were pains in the left or right shoulder of "inactivity" or periarthritis type without simultaneous general symptoms and without other effect on the circulatory or respiratory organs. Thus in these cases it was not a matter of a PCS syndrome of the type here in question. These six cases are therefore dismissed from the discussion in the sequel.

Of the remaining 10 patients, nine had secondarily appearing pains localized to the left shoulder region and/or the region between the shoulder and the operation wound. One remained entirely free of pain. There was no palpation tenderness over the shoulder joints. All 10 had at the same time a considerable increase of the general symptoms and in the local symptoms from heart and lungs.

The symptoms were acutely exacerbated 2–3 weeks after the valvulotomy. In three cases there were two periods of such discomfort with intermediate intervals of about two weeks without symptoms. The symptoms may be summarized as follows.

The *temperature* rose regularly to varying values. In seven of the ten cases maximum values of 39°C and more were reached. This temperature peak was as a rule of short duration and was succeeded by a lytic fall. One single patient was subfebrile the whole time, with a temperature below 38°C. Also in this case, however, there was a distinct secondary rise in temperature in connection with PCS.

The *sedimentation rate* varied. It was as a rule sinking after the operation when PCS was first manifested. In all cases except one there was in this connection a secondary rise in SR varying in magnitude between 7 and 37 mm in relation to the immediately preceding SR value before the manifestation of PCS.

The *leucocyte value* showed in general a slight rise in connection with the rise in temperature.

The *pains* were as a rule intense and at times disturbed the patients' sleep at night. In two cases it was necessary at times to administer analgesics of morphine type to alleviate the pains. They were described as a dull ache, more or less like toothache. They abated slowly in the course of a week. In two cases they occurred in the course of cortisone therapy.

Pleural exudate always appears after the operation, but is generally quickly resorbed. In the cases described here a secondary increase in the amount of fluid was found in connection with PCS. In one case there was even a very pronounced increase of exudate necessitating thoracocentesis. The exudate was in this case clear and dark amber-yellow, and contained a rather sparse scattering of mononuclear cells. In the other cases the exudates were relatively small and were resorbed spontaneously.

The *pericardial exudates* were diagnosed in the course of the routine X-ray control of the thoracic organs. These were in all cases "small" exudates from the roentgenological point of view. Since a roentgenological diagnosis nevertheless presupposes a rather considerable amount of exudate, the frequencies observed for this complication are to be regarded as minimum values. There were no tamponade symptoms.

The *pulse rate* increased in connection

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Early Diastolic Murmur in a Case of Infundibular Stenosis of the Right Ventricle

STURE BEVEGÅRD, BENGT JONSSON and ULF RUDHE

Pulmonary stenosis with intact ventricular septum was formerly a relatively unknown malformation. It is now about ten years since its clinical features were described by various authors, and today it is a well-established pathologic entity, which can usually be diagnosed on the basis of the physical findings alone. As a rule, the stenosis is valvular. In combination with ventricular septal defect, on the contrary, the stenosis is most often infundibular. Cases are, however, found of infundibular stenosis with intact ventricular septum. In a series of 45 cases of pulmonary stenosis with intact ventricular septum studied at the Paediatric Clinic, Karolinska Sjukhuset, infundibular stenosis alone was present in 4 (Kjellberg, Mannheimer, Rudhe & Jonsson, 1959). In such cases, the stenosis is localized to the ostium infundibuli, and is due chiefly to displacement of the septal band of the crista supraventricularis.

The most important physical finding is a systolic murmur, which usually has its maximum over the 3rd left interspace. We have not earlier observed a diastolic murmur in such cases, nor has any been described in the literature. Consequently, it was surprising to find a short, high-frequency murmur in early diastole in a patient with mild infundibular stenosis. The occurrence of the murmur could, however, be explained by subsequent analysis of the haemodynamic conditions by cardiac catheterization and electrokymography.

The methods used for phonocardiography and electrokymography have been described in earlier reports from the Paediatric Clinic (Mannheimer, 1955; Rudhe, 1956). Those applied in cardiac catheterization and determination of the physical working capacity have been reported from the Department of Clinical Physiology (Jonsson, Linderholm & Pinardi, 1957).

CASE REPORT

The patient was a 52-year-old man (catheterization no. 9/59). His physical working capacity was very good, i.e., 1200 kgm/min. Heart volume was normal. The ECG showed no hypertrophy, but the S–T interval was depressed, which may have been due to digitalis medication, given until

1955) or, possibly, cases of recurrent idiopathic pericarditis (Dressler, 1954).

The etiology may of course vary in different cases. Of this we know nothing. "Idiopathic recurrent pericarditis" is an uncommon condition and it is therefore not reasonable to refer the main part of PCS to this disease. Exacerbation of the etiological process is rather contradicted by the absence of other rheumatic manifestations. Furthermore, the course of the symptoms was in general of too short a duration and too benign to make the assumption of rheumatic relapses probable. The protracted cortisone therapy applied to a part of the clientèle may, certainly, have masked some cases of rheumatic activity. The majority, however, were not given cortisone treatment. The selection of patients for cortisone treatment was entirely a matter of chance, as all patients operated upon from a certain period were given cortisone in the postoperative period. There are also 2 clear PCS cases in the group of 33 patients who were given cortisone therapy. As against these we have 8 PCS among the 73 patients who were not treated with cortisone. The difference in frequency is not significant ($P = 0.50$–0.30).

There is, on the other hand, nothing in our results to contradict the assumption that PCS was released by local irritation factors in the operative area or its immediate vicinity. It may have been a matter of small hemorrhages, where the blood has functioned as an irritating agent in the pleura and pericardium. The whole clientèle was put on dicumarol therapy about 1 week after the operation.

The frequency of PCS in our material is 10/106 = 9.4 %, which is in fairly good agreement with the 10 % "postoperative pericarditis with fever" among operated mitral stenoses reported by Wood (1954).

SUMMARY

1. PCS appeared in 10 of 106 patients who had been operated upon for mitral stenosis.

2. The syndrome was characterized by a temporary secondary exacerbation of the postoperative symptoms, with fever, heightened SR, exudate in the pleura and/or pericardium and in general pains in the region of the left shoulder.

3. In 2 cases the syndrome appeared among a group of 33 patients who were undergoing postoperative cortisone treatment.

4. In a number of cases the condition caused considerable subjective discomfort with very appreciable pains.

5. The prognosis was in all cases good.

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in the pressure curve from the pulmonary artery, it is difficult to localize exactly the time of closure of the pulmonary valve. It is, however, possible on the basis of the phonocardiogram, recorded at the same pulse rate, to fix closure of the valve at point 1 in Fig. 1, which coincides with the time when the pressure in the infundibulum falls below that in the pulmonary artery. Thus, between points 2 and 3—when the pressure in the infundibulum is lower than in the pulmonary artery, but higher than in the sinus portion of the right ventricle—the prerequisites exist for a retrograde flow through the infundibular stenosis. On comparison with the phonocardiogram, this time interval is seen to correspond to the time of appearance of the diastolic murmur. This is because points 2 and 3 occur 0.40 sec after the *Q* wave on the ECG, and the murmur starts 0.40 sec after this wave.

With a view to obtaining further information regarding the origin of the murmur, the variations in volume of the different heart chambers during the cardiac cycle were studied electrokymographically, with synchronous recording of the ECG and phonocardiogram. In order to reproduce the variations in volume as accurately as possible, they were recorded densographically. The photocell of the electrokymograph was thus placed completely inside the border of the relevant heart chambers. Consequently, on the curves obtained, the influence of such movements as are not directly dependent on emptying and filling of the chambers can be regarded to be reduced to a minimum. The photocell was moved stepwise from the upper part of the infundibulum to the lower part of the sinus portion of the ventricle. Curves were also recorded over the right atrium. The examination was performed in the accentuated right anterior oblique projection, which on anatomic grounds is best suited for visualization of the heart chambers without superimposition.

It can be seen from Fig. 2 that filling of the sinus portion of the right ventricle starts a few hundredths of a second after the pulmonary component of the 2nd sound. During the subsequent first part of diastole, the infundibulum continues, on the contrary, to decrease in volume.

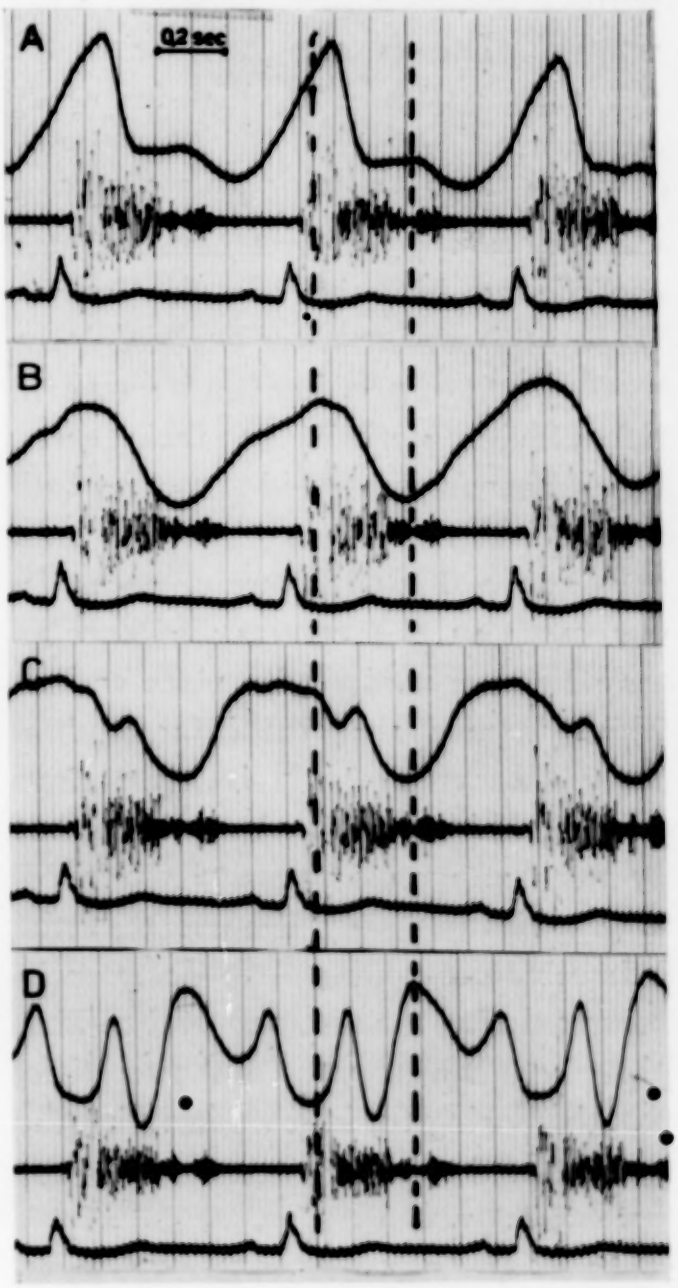


FIG. 2. Electrokymograms recorded synchronously with the ECG and phonocardiogram (over 4th L.I.S.). Electrokymograms recorded as densograms. A downward movement denotes a decrease in volume, and an upward movement an increase. Time lag of electrokymogram: 0.01 sec. *A*, infundibulum; *B*, upper part of sinus portion of right ventricle; *C*, lower part of sinus portion; *D*, right atrium. Left broken line coincides with end of 1st sound and marks start of emptying of right ventricle, as is evident from *C*. Right broken line denotes opening of tricuspid valve (*D*), corresponding to start of filling of right ventricle (*C*).

It is evident from these densographic electrokymograms that infundibular contraction (*A*) starts after expulsion of blood from sinus portion. During first part of diastole, there is a further reduction in volume of infundibulum, coinciding with appearance of diastolic murmur. This is synchronous with expansion of sinus portion of right ventricle. The curve recorded over upper part of sinus portion (*B*) shows an intermediate movement pattern during start of ejection.

TABLE 1. Findings at cardiac catheterization.

Body weight = 63.9 kg. Height = 163.5 cm. Body surface area = 1.69 m².

	O_2 saturation, %					O_2 uptake,	Pulse rate,	$AV-O_2$ diff.,	Cardiac ouput,	Stroke vol.,	Pressure, mm Hg				
	Br. art.	SVC	RA	RV	PA	ml/min	beats/min	ml/l	l/min	ml	RA	RV sinus	RV infund.	PA	Br. art.
At rest	97	71	79	72	72	284	79	42	6.8	86	0	43/2	26/2	26/11	120/63
300 kgm/min	95	—	—	—	54	1066	111	79	13.6	121	2	84/6	—	42/17	158/81
600 kgm/min	96	—	—	—	45	1599	138	104	15.3	111	2	105/10	—	38/15	190/85
900 kgm/min	93	—	—	—	32	2146	167	129	16.6	99	—	123/12	—	42/18	—

admission to hospital. Fig. 1*C* shows the phonocardiogram recorded over the 3rd L.I.S. An early systolic sound appears 0.06 sec after the 1st heart sound, accompanied by a systolic murmur which ends with the aortic component (*a*) of the 2nd sound. The pulmonary component (*p*) occurs 0.06 sec later; 0.03 sec after it (0.40 sec after the *Q* wave on the ECG), a high-frequency, diamond shaped murmur starts, and has a duration of about 0.08 sec. This murmur has its maximum here.

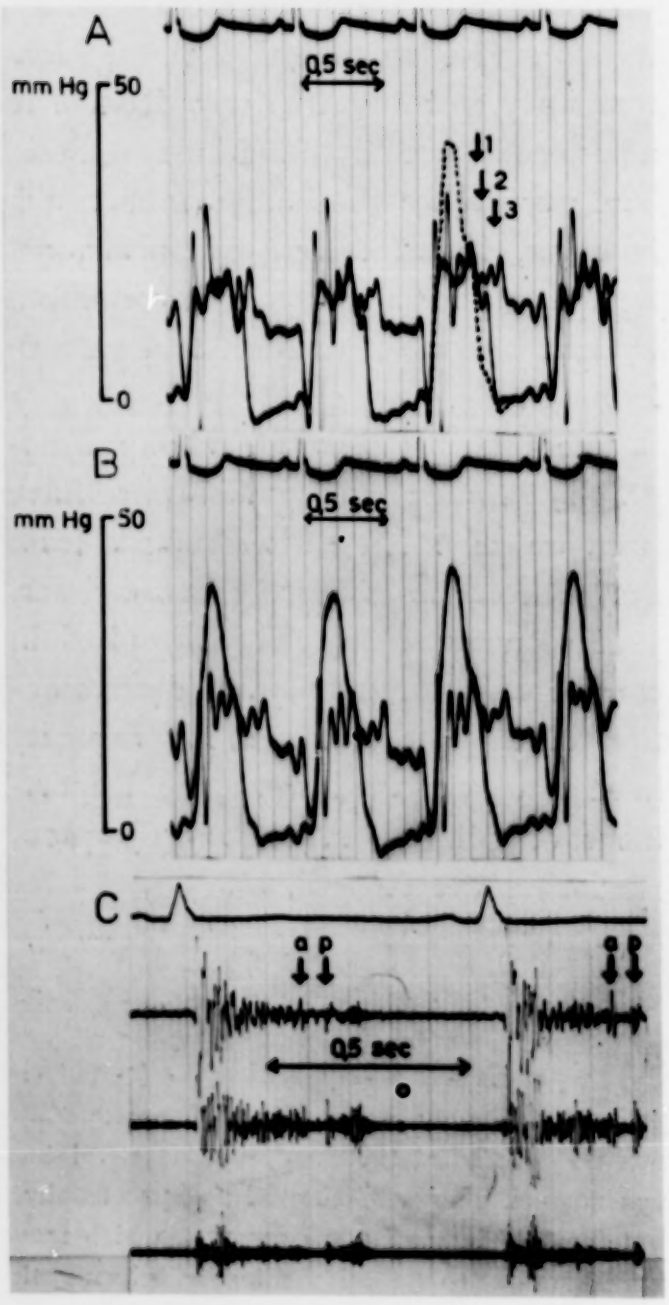


FIG. 1. Simultaneous pressure recording from main trunk of pulmonary artery and infundibulum of right ventricle (*A*), from main trunk of pulmonary artery and sinus portion of right ventricle (*B*), and phonocardiogram recorded over 3rd L.I.S. (*C*). Same pulse rate in all recordings. In *A*, the broken line denotes the pressure in the sinus portion. At *1*, closure of pulmonary valve. Between *2* and *3*, the pressure in the infundibulum is lower than in the pulmonary artery, but higher than in the sinus portion. The diastolic murmur occurs during this period. *a* = aortic component of 2nd heart sound, *p* = pulmonary component.

The findings at cardiac catheterization can be inferred from Table 1. No signs of a shunt were present. There was a systolic pressure gradient of 23 mm Hg at rest between the sinus portion of the right ventricle and the infundibulum. With a heavy work load (pulse rate 167/min), the gradient rose to 81 mm Hg. No pressure gradient was present between the infundibulum and the pulmonary artery.

Analysis of the pressure curves from the pulmonary artery, infundibulum and sinus portion of the right ventricle (Fig. 1 *A* and *B*) shows that systole has a longer duration in the infundibulum than in the sinus portion. Consequently, during a brief period (from point 2 to 3 in Fig. 1), the pressure is higher in the infundibulum than in the sinus portion. Owing to numerous vibrations

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Myxoma of the Left Auricle

A Report of Three Cases

OLOV CELANDER, GÖRAN LINDQVIST and RAOUL MALMCRONA

A myxoma in the left auricle was in 1954 operated successfully for the first time by Crafoord and Senning. As the disease had been considered extremely rare and without possibility of treatment, little practical importance had earlier been ascribed to these tumours. Since several cases of successful operation have now been reported (Chin & Ross, 1957; Harvey, 1957), stricter diagnostic criteria are called for. Successful surgery in cases of cardiac myxoma requires exact diagnosis, as the risk of operative failure is otherwise great (Bailey, Lacy & Harris, 1951; Davies & Andrus, 1954; Likoff, Gelecker & Gregory, 1954).

A myxoma in the left auricle obliterating the mitral ostium gives a symptom complex in close agreement with that found in mitral stenosis. However, the disease often shows features which ought to make it possible in many cases to arrive at a correct diagnosis before the exploration. We have observed and followed 3 cases of the disease and shall here discuss the features in the histories and the clinical findings that may afford possibilities of diagnosing the condition. Furthermore, about 50 cases from the literature have been reviewed with reference to the characteristic features of the disease.

CASE REPORTS

Case 1

Glass-works employee, born 1915. No known rheumatic affection. Had long-distance rowing as hobby up to 1955. After this date increasing dyspnea in connection with exertion and asthma-like trouble at night. Medical examination in September 1956 revealed a cardiac murmur, anemia and high SR. Admitted to the local hospital where he was described as "pale and fatigued". Examination revealed presystolic crescendo murmur, accentuated 1st cardiac sound, and blood pressure 150/90. Hb 70 %, SR 27 mm. ECG normal. X-ray showed size of heart 600 ml/m^2 body-surface with enlargement of left auricle. Patient improved and returned to full-time work. Was relatively free of symptoms apart from dyspnea in connection with exertion and obscure peaks

This is accentuated during the interval marked by the diastolic murmur. It is not until after this that the infundibulum once more expands.

DISCUSSION

An analysis of the variations in pressure and volume in the pulmonary artery, as well as in the infundibulum and sinus portion of the right ventricle, has shown that the infundibulum remains contracted for a longer time than the sinus portion. Moreover, the flow through the infundibular stenosis then passes in the retrograde direction, i.e., from the infundibulum to the sinus portion, during a short period in early diastole. This is associated with the appearance of a short, high-frequency murmur.

The delayed contraction of the infundibular chamber has been demonstrated earlier by Mannheimer & Jonsson (1954), this circumstance explaining the marked splitting of the 2nd sound in infundibular stenosis. In their cases, the pulmonary valve did not close until after relaxation of the infundibulum, nor did any diastolic murmur occur. In our case, on the contrary, closure of the pulmonary valve took place earlier, which implied that the infundibulum could then empty only into the sinus portion. This interpretation is borne out by the densograms recorded electrokymographically. They showed that the infundibulum continued to decrease in volume during the first part of the filling phase in the sinus portion of the ventricle, namely, during the interval in which the diastolic murmur appeared. It is possible that the changes in elasticity of the arteries, as well as in the resistance in the pulmonary circuit, associated with rising age may be responsible for earlier closure of the valve. It is not known whether this patient also exhibited a diastolic murmur when he was younger.

SUMMARY

An account is given of an unusual finding in a patient with mild infundibular stenosis, namely, an early-diastolic murmur. An analysis has been made of the variations in pressure and volume in the infundibulum and sinus portion of the right ventricle during the cardiac cycle. It shows that the murmur can be explained by a retrograde flow through the stenosis, i.e., from the infundibulum to the sinus portion, during a short period in early diastole.

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period subfebrile. She lost 5 kg in weight and after three weeks was discharged under the diagnosis VOC mitrale. Was then relatively free of subjective symptoms but was readmitted after a month as she had had repeated attacks of pulmonary edema. During this stay in hospital the murmurs varied greatly, being sometimes entirely absent and on other occasions comprising systolic as well as previously unnoticed diastolic murmurs. She was at first subfebrile. SR was high, maximally 68 mm. AST and repeated blood cultures normal. ECG showed only minor changes. PhCG showed over the apex a weak presystolic murmur, a systolic murmur and a doubled 2nd sound. In left I_4 a weak protodiastolic murmur was recorded. Electrokymography showed a picture resembling that in "mitral stenosis with pulmonal hypertension" (later scrutiny, however, revealed suspect variations over the left auricle). Endocarditis lenta appeared probable. Patient's state became progressively worse. During the last period the patient was observed trying to alleviate her dyspnea by lying face downwards with her head low; and she mentioned that she had also previously adopted this procedure. The existence of myxoma in the left auricle was now suspected, but the patient's state did not permit of any further investigation. She died in February 1955.

Autopsy showed hypertrophy of left ventricle and dilatation of left auricle. On the medial wall in the left auricle was a tumour almost the size of a hen's egg, with broad attachment (Fig. 1) and with one pole bulging down through the mitral ostium, where it was somewhat

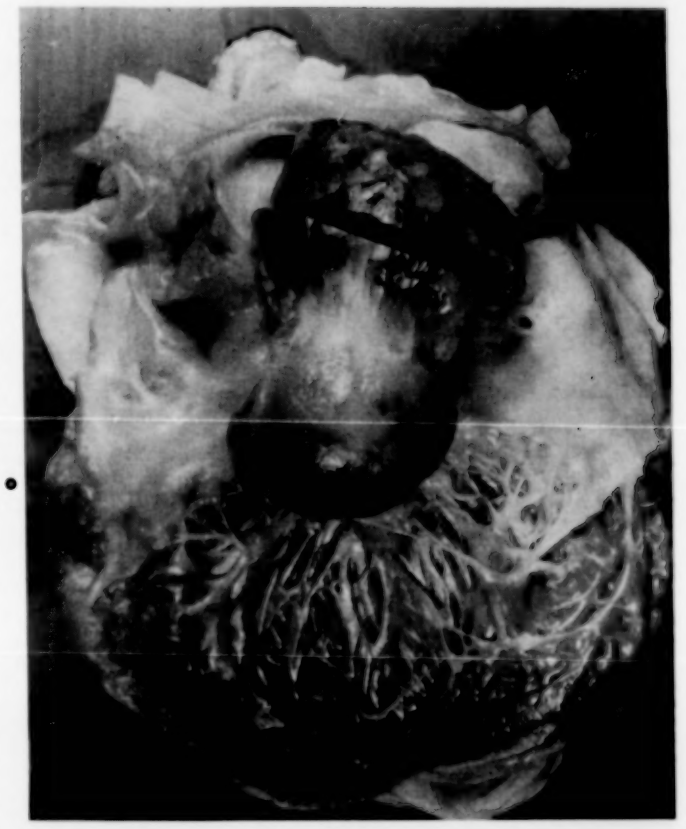


FIG. 1. Myxoma in left auricle. Note especially the "waist" corresponding to the mitral ostium. Case 2.

constricted. The surface was even, in part calcareous. The consistency was firm and the section translucent with alternating yellow and blood-stained areas. All valves and ostia were normal. A number of infarcts were observed in the lungs. Microscopic examination showed "so-called endocardiac myxoma".

Case 3

Woman born 1913. Husband factory worker. Five small children. No known rheumatic affection. Healthy up to January 1952, when she began to notice fatigue, shortness of breath and palpitations in connection with exertion. Digitalization without improvement and admitted in July 1952. Had then good general condition and absence of signs of incompensation in state of rest. Over the apex was heard a short systolic and

of fever after strenuous work. Controls showed persisting moderate anemia and heightened SR.

In April 1958 admitted to the Sahlgren Hospital, Gothenburg, for examination and decision regarding operation under the diagnosis mitral stenosis. His general condition was at that time relatively good and he was without signs of incompensation. Heart status on the whole the same as previously but in addition accentuated 2nd sound over pulmonalis. Hb 10–11 g%. ECG indicated right heart strain. PhCG: feeble presystolic murmur of low frequency, nothing definite systolically but 0.12 sec. after the 2nd sound a short diastolic murmur of low frequency. X-ray: size of heart 770 ml/m^2 body-surface with enlargement mainly of left auricle but also left ventricle. Electrokymography showed "picture as in combined mitral defect" (later scrutiny, however, revealed suspect variations over left auricle). With load to 600 kgm/min. the heart rate rose to 150. The patient was relatively free of subjective symptoms, but after load ECG revealed moderate ST and T changes. Heart catheterization showed increased pressure in the pulmonary circulation which was further accentuated with load of 200 kgm/min. Pressure in AP in state of rest 96/49, during work 121/50 and in PCV in state of rest 35 mm Hg. Under load the stroke volume diminished and the AV–O_2 difference increased. The case was diagnosed as "relatively pure mitral stenosis" and the patient was advised to undergo operation. However, this was postponed until October 1958 on account of the unclear anemia and the heightened SR. He went back to work and, as before, became short of breath when he exerted himself, but was otherwise relatively without discomfort.

On operation a resistance the size of a large plum was found in the left auricle, obstructing the mitral ostium and attached to the lateral auricular wall with a pedicle as thick as a finger. On attempts to palpate the mitral valves the greater part of the tumour loosened and followed the blood stream. It was found on subsequent operation in the aortal bifurcation. The patient died 3 days later in a picture of multiple thrombosis and emboli.

Autopsy revealed normal mitral valves. Microscopically the tumour-tissue showed a picture resembling that of endocardiac myxoma.

Case 2

Cook, born 1902. One grown-up child. No known rheumatic affection. Healthy up to November 1953, when after a cold she developed persisting cough with admixture of blood in expectorated matter and increasing shortness of breath in connection with exertion. In the summer of 1954 cardiac murmur was observed and X-ray examination showed size of heart to be 770 ml/m^2 body-surface, stasis in the pulmonary circulation and fluid in the right pleura. She was admitted for examination and had at that time a good general condition, slight dyspnea in state of rest, hepatic swelling and rales at both lung bases. Broadened ictus. Strong systolic murmur with P.M. in I_3 sin. Second sound divided over pulmonalis. Sinus rhythm. Was during first

fluid in both pleurae. Her condition gradually deteriorated and she died in March 1954 after periods of fever, varying degrees of incompensation, anemia and heightened SR.

The course of the ECG changes in this case is illustrated in its main features in Fig. 2. There gradually developed a right preponderance and enlarged P peaks. Transient fibrillation began to occur after scarcely one year's anamnesis, and during the last months there were still frequent alterntions between fibrillation and sinus rhythm. During the last period there was constant bigemina and on the last day a very protracted conduction time. The clinical diagnosis was mitral stenosis and mitral insufficiency. By the criteria then applying she was at an early stage considered unsuitable for operation.

Autopsy revealed a smooth tumour the size of a hen's egg attached by a short pedicle to the auricular septum in the vicinity of foramen ovale. The surface of the tumour was smooth and jelly-like, but in a short time it became opaque. The consistency was firm. Section was yellow, jelly-like with blood-stained streaks. Microscopically the tumour showed the picture of fibroangiomyxoma with pronounced myxomatous components. All valves and ostia normal. In the lungs several infarcts and in the right pulmonary artery large thrombotic masses. Chronic stasis liver with incipient cirrhosis.

DISCUSSION

The not infrequent cases in which in connection with a preoperative examination or the operation of mitral stenoses a cardiac myxoma has been found give grounds for the assumption that these heart tumours are commoner than emerges from the literature. It is probable that the relative frequency of cardiac myxoma in relation to mitral stenosis will increase, against the background of the fact that in recent years rheumatic fever has become increasingly uncommon and with a lesser number of sequelae in the form of rheumatic valve defects.

The pathologists have shown great interest in cardiac myxoma and have in this connection occupied themselves chiefly with the question of the systematic placing of these tumorous formations. A number of such writers have asserted that myxoma is an independent form of tumour, while others have been inclined to understand the auricular myxoma as wall-attached thrombi that have undergone myxomatous degeneration. This question is from the clinical point of view of relatively little interest, since in both cases there is probably the risk of recidivation if the tumorous formation is not radically removed. We shall here refer to these formations as tumours without considering their pathogenesis more closely. A clinically more important factor is the great variability in the form and consistency of the tumours. The firm tumours are as a rule egg-shaped, in some cases in combination with a furrow corresponding to the mitral ostium where the tumour partly hangs down into the left ventricle (case 2). These tumours are as a rule at least the size of a hen's egg when they can be assessed as operable. The soft and looser tumours are often

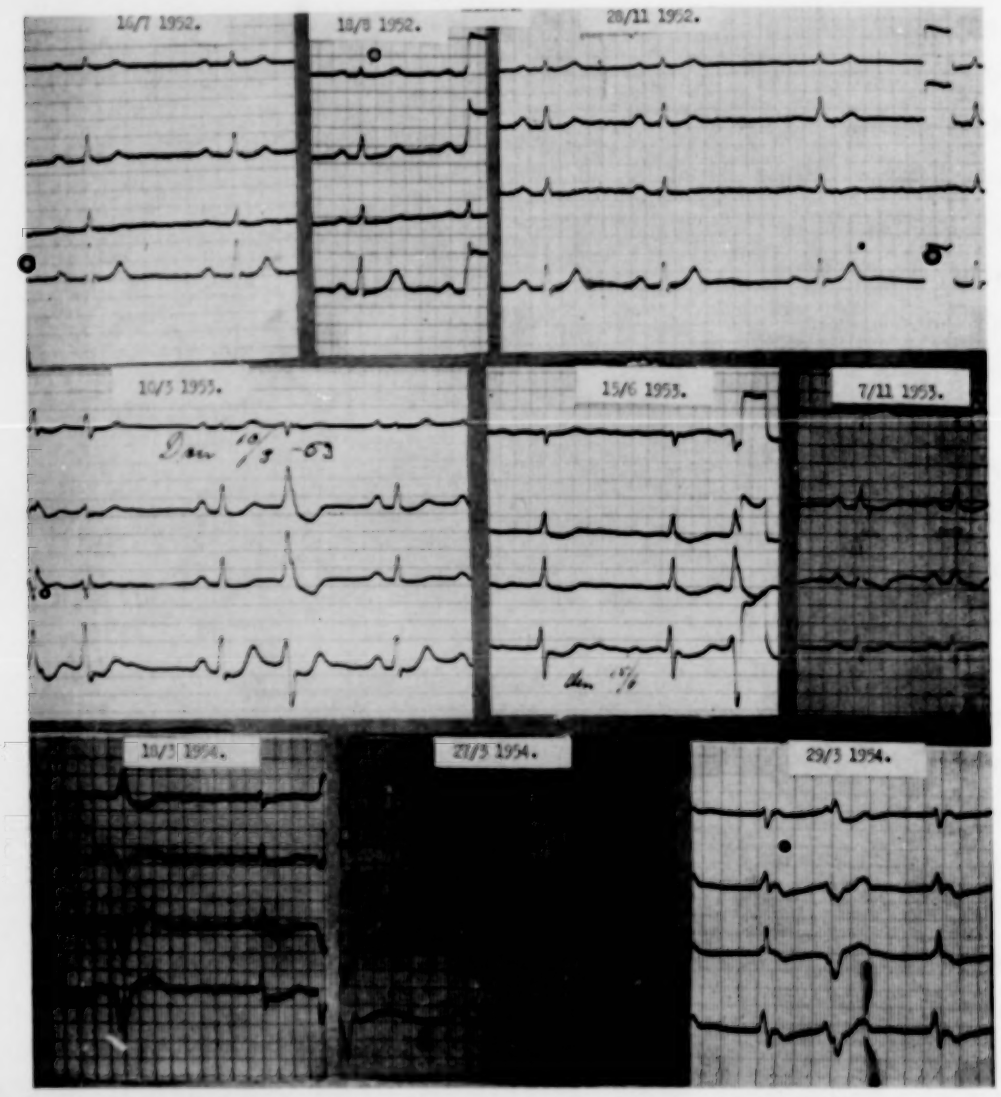


FIG. 2. Electrocardiographic findings in case 3.

a clear presystolic murmur. Only in the recumbent position was a diastolic murmur also audible. The first heart sound was accentuated and the second divided. No fever. Hb and SR normal. X-ray showed size of heart to be 515 ml/m^2 body-surface with enlargement of left auricle. Digitalis did not give any effect, even in increased dose, and was discontinued. After two weeks' stay in hospital nursing was continued at home. Her symptoms were sometimes only slight, but at times signs of incompensation were observed even in the state of rest. In April 1953 she fell ill with high fever and a sensation of stitch in the breast. She was readmitted in a general condition that was slightly affected. Had dyspnea in state of rest, labial cyanosis and enlargement of the liver. During next few months she had several periods with high fever. Heightened SR up to maximally 67 mm was noted, in between normal SR. X-ray showed size of heart to be maximally 670 ml/m^2 body-surface and on a couple of occasions indurations over both lung bases and fluid in pleurae. For a period thrombosis in left calf. Her state was improved and stabilized so that she could return home, though she had not the strength for housework. Another deterioration led to her readmission in November 1953. She then had cyanotic lips, dyspnea in state of rest, considerable peripheral edema, hepatic enlargement and exudation of

TABLE 1. First symptoms in 31 cases of myxoma in the left auricle.

(One or two symptoms have been indicated in the different cases.)

Symptom	No.	Symptom	No.
Dyspnea	12	Giddiness	2
Palpitations	5	Syncope	1
Fatigue	5	Cough	1
Arterial embolism	3	Acute pulm. edema	1
Tachycardia	3	Precordial pain	1
Peripheral edema	3	Emaciation	1
Infection of respir. passages	2		

that the degree of physical invalidity and the clinical findings show a slowly progressive course. In myxoma cases we find, in contradistinction to this, an irregular and at the same time often more rapid development. The patient dies as a rule within three years from the appearance of the first symptoms. The irregular development may be due to the fact that the tumour changes its position in relation to the ostium, thus giving rise to a variation in the auscultatory and other clinical findings. That the patient changes his body position may be conceived to result in sudden changes in the position of the tumour. This was obviously the situation in our second case, where the patient was able to alleviate her dyspnea by lying face downwards with her head low. This "paradoxical orthopnea" has previously been described in the literature (McAllen, 1950; Desbaillets, Wyss & Mahaim, 1953; Martin, 1953). This behaviour contrasts strongly with the characteristic orthopnea of the mitral stenosis patients. Our third patient showed at the beginning of the pathological development surprisingly pronounced and rapid variations in the degree of the heart trouble independently of the therapy. Such a marked variability in the degree of the symptoms has also been mentioned in the literature (Mahaim, 1945). The symptom of quadripedal ischemia described by, inter alia, Ask-Upmark occurs relatively seldom, but may nevertheless be stated as typical of the disease (Field, Donovan & Simon, 1945; Brewin, 1948; McAllen, 1950; Ask-Upmark, 1952; Mahaim, 1953). Acute attacks of syncope are reported to be a common symptom (Mahaim, 1945).

The tendency of the tumorous formations to drop fragments resulting in arterial emboli may lead to sudden death or symptoms from different sections of the systemic circulation (Mahaim, 1945; Brown, 1946; Brewin, 1948 and 1951; Weinstein & Arata, 1949; Lampen & Waag, 1951; Blum, 1952). Emboli occur also in cases of mitral stenosis, and they can thus not be said to constitute a specific symptom (Olesen, 1955). In our first case the patient had unclear feverish reactions in connection with exertion. It is possible that the increased rate of circulation connected with physical exertion led to the breaking off of small fragments of the tumour.

In all of our cases pulmonary emboli occurred as an important feature in the anamnesis. In case 3 these probably emanated from her peripheral thromboses, but in the two other cases no signs of such thromboses were observable. In these cases pulmonary emboli may have emanated from thrombotic material in the right auricle. Such thrombi in the right auricle have been described (Burnett & Davidson,

lobate or lobulated. Among our cases the first was a soft and easily disintegrating formation, while the tumours in cases 2 and 3 were firm and had a smooth surface. Of 42 cases in the literature, 17 show an even surface and, where there was mention of the consistency, it was firm in these cases. In 12 cases the surface was somewhat lobate, while 13 cases showed varying degrees of lobation. In those cases in which the tumour has had a firm consistency the tumour diagnosis has been more easily accepted, while with loose and irregular tumours the tendency has been to regard them as organized thrombi. Of the greatest importance for the course of the disease is the fragility of these tumours and the consequent tendency to drop fragments in the form of arterial emboli.

The course of the disease in cases of myxoma in the left auricle varies. In certain cases the patient may rather suddenly succumb from large arterial emboli after complete freedom from symptoms or a short period of insignificant symptoms (Mahaim, 1945; Brewin, 1948 and 1951; Blum, 1952). Other tumours, above all smooth and firm tumorous formations, have, instead of this course, a more protracted development which allows scope for a complete investigation.

Before one is justified in discontinuing the investigations on the preliminary diagnosis of mitral stenosis one must be able to rule out cardiac myxoma. This is exemplified by our third case, which was regarded as an inoperable case of mitral stenosis. There would probably have been a good chance of removing her cardiac myxoma by surgery.

In cases of myxoma earlier rheumatic fever or other evident etiological explanation of a traditional mitral stenosis does not occur in the anamnesis. Among mitral stenoses, on the other hand, there is a high percentage of previous rheumatic affections (Olesen, 1955). It is of course possible to meet with purely coinciding cases of the two diseases (Dexter & Work, 1941; Weinstein & Arata, 1949).

It is worth noting that in cases of cardiac myxoma the previous capacity for work has been good in a striking degree. This applies in a high degree to our three cases. Thus the first patient was able to row long distances right up until three years before his death. Patient number 3 had given birth to five children and managed a big household without trouble.

The age at which the first symptoms of cardiac myxoma appear is, disregarding myxoma in early childhood, somewhat higher than that found in a mitral vitium clientèle. The difference is, however, so inconsiderable that in the individual case one is not much helped by this circumstance.

Table 1 represents a tabular presentation of the first symptoms in 31 cases of myxoma in the left auricle. Dyspnea due to exertion and palpitations are also the most important symptoms in mitral stenosis (Olesen, 1955). A tumour obstructing the mitral ostium must obviously affect the blood flow in the left side of the heart and the pulmonary circulation in the same way as does the obstruction to the flow constituted by a mitral stenosis. The mitral stenosis, however, implies a slowly increasing hindrance to the circulation. This means

and considerable variability with regard to the appearance of the auricular evacuation curve was therefore not then taken into account. A report of these observations will be published separately (Bartley).

Case 1 was made the object of heart catheterization with a study of the hemodynamics in the pulmonary circulation both at rest and during work. The findings are in good agreement with what one expects in cases of mitral defect. Unfortunately recordings were not made in different body positions.

SUMMARY

Certain features in a case history should give rise to the suspicion of myxoma in the left auricle. The absence of earlier rheumatic affection, relatively rapidly increasing subjective symptoms in a person with previously for the most part good physical capacity, symptoms showing striking variability and not appreciably influenced by digitalization or other measures against cardiac insufficiency—all these are features distinguishing the history in cases of cardiac myxoma from what one generally finds in cases of mitral stenosis. Obscure feverish periods and high SR frequently occur, probably related to different manifestations of thrombosis and arterial emboli.

To variability in the patient's subjective symptoms corresponds the tendency of the tumour to constrict the mitral ostium in varying degrees. In cases in which the recumbent face-downward position is preferred to the sitting position cardiac myxoma may be strongly suspected. The EkyG affords the possibility of a detailed analysis of the course of evacuation in the left auricle, which may help in arriving at a diagnosis (Bartley).

Myxoma in the left auricle has formerly been considered of only academic interest. With the development of heart surgery the tumours came to constitute a fatal source of error in connection with the operation of mitral defects. A surgeon suspecting a mitral stenosis but confronted with an easily disintegrating tumour and normal mitral valves has small possibilities of coping with the situation. With an exact diagnosis, on the other hand, there is a fair chance for surgery in cardiac myxoma.

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1945; Lampen & Waag, 1951; Ask-Upmark, 1952; Blum, 1952; Raeburn, 1952; Örndahl & Örndahl, 1954). Increased tendency to the development of thrombosis may exist as a common etiological factor for myxoma and thromboses. The changed hemodynamics may also possibly facilitate the formation of thrombi.

Variability in auscultatory findings should give rise to the suspicion of cardiac myxoma. The prerequisite for this, however, is often repeated and carefully reported examination of the heart. Further, the possibilities of a correct diagnosis are increased if the examination is undertaken with the patient in different body positions. In all our cases variations in the diastolic murmur over the apex were observable. Similar variations are reported in the literature (Mahaim, 1945). In 35 cases of myxoma from the years 1945–1955 with an account of the heart status there were systolic murmurs in 25 cases. In 22 cases diastolic murmurs of different types and degrees were observable. In 2 of the cases the systolic murmur was stated to have been inconstant, while the diastolic murmur was described as variable in 11 of the cases. In only 2 cases was a variation due to position described (Kirkeby & Leren, 1952; Steinberg, Dottner & Glenn, 1953). In our third case the murmurs were clearly influenced by the position of the patient.

Fever and a heightening of SR are frequently noted in cases of cardiac myxoma. In our first case this gave rise to the suspicion of malign disease and in the second of current endocarditis lenta. The background to these symptoms is probably often constituted by thromboses, pulmonary emboli and possibly minor arterial emboli.

In our second case blood cultures were made on several occasions with negative result. Positive results have, however, been reported in the literature (Dick & Mullin, 1956). It seems natural that these tumours, just as well as pathologically changed valves, should be seats for infection.

Of particular interest from the point of view of the ECG is our third case (Fig. 2). When seen against the background of the autopsy findings it is easy to understand the picture of symptoms here: a large myxoma attached to and immediately adjacent to important elements of the conduction system. Right-sided preponderance, minor P-peak changes and fibrillation are otherwise the findings most commonly reported in the literature.

In none of our cases did X-ray examination reveal anything markedly deviating from the traditional findings in cases of mitral defects with stasis in the pulmonary circulation. Only in case 2 were the possibilities of angiocardiography discussed, but the patient's condition was considered to contraindicate this examination. It is reported (Goldberg & Steinberg, 1955; van Buchem & Eerland, 1957) that even venous angiocardiography can give important information. Left-sided angiocardiography gives the diagnosis.

In our first two cases electrokymography was performed. On the occasions of the examinations, however, the notion of the possibility of a tumour in the left auricle had not been entertained,

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From the Thoracic Clinic, Karolinska Sjukhuset, Stockholm, Sweden

Penetrating Heart Wounds with Hemopericardium

STIG EKESTRÖM och ADAR HALLÉN

We have recently treated two cases of hemopericardium on a traumatic basis. In both cases, the foreign body responsible was still present. Both patients were operated on, and have completely recovered. In penetrating wounds of the heart, the picture is most often dominated by the hemopericardium. This condition, which is not so uncommon, presents such interesting features from the physiologic, diagnostic and not least the therapeutic aspects, that we have considered a report of these cases to be warranted.

CASE REPORTS

Case 1.—A 46-year-old woman. During a meal, there was a sudden onset of pain, first at the level of the larynx and then in the epigastrium, when she swallowed a bolus. Two days later, increasing pain appeared behind the sternum, radiating into the back between the shoulder blades and up towards the ears, as well as a stabbing pain on respiration. Roentgenologic examination disclosed a "needle-shaped foreign body" directly beside the heart, approximately at the site of the right atrium. Fluoroscopy showed decreased movements of the pericardium, as in the presence of effusion. Signs of pericarditis were present on the ECG. Signs of venous congestion in the form of engorged neck veins were, however, lacking.

Thoracotomy was performed four days after the injury. A moderate increase in fluid was found in the pericardium. The connective tissue around the esophagus was blood-stained. The pericardium was distended, and its movements in connexion with the heart contractions were greatly limited. After incision of the pericardium, about 200 ml of markedly hemorrhagic fluid were aspirated. A pin, which penetrated the pericardium, was then removed. The postoperative course was completely uneventful.

Case 2.—A 40-year-old man, previously healthy. When he was sawing wood, a piece of wire rebounded and penetrated the left side of the chest wall. The patient was able to cycle 5 km to the nearest hospital, where a small opening was found on the left side of the anterior chest wall. Roentgenologic examination showed a piece of wire probably lying in the wall of the right atrium. Neither pneumothorax nor pleural effusion was present. The patient was immediately referred to our clinic.

On admission, his general condition was unaffected, but he complained of pain in the lower jaw. There was no cyanosis or dyspnea. Auscultation showed nothing noteworthy in the heart or lungs. Blood pressure 130/90 mm Hg. No engorgement of the neck veins. The ECG showed generalized elevation of the S–T interval, and changes indicative of pericarditis subsequently appeared. Roentgenologic examination disclosed nothing pathologic apart from the foreign body in the wall of the right atrium. On the other hand, fluoroscopy showed a quiet heart, i.e., absence of pulsations.

Right-sided thoracotomy was performed on the day after the injury. Our indications for operation were the presence of a foreign body in the right atrial wall, with the associated risk of hemorrhage

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the essential factor is the impeded inflow to the heart from the systemic veins, as a result of their obstruction. Isaacs *et al.* were, however, able to show that in experimentally induced cardiac tamponade, there is no measurable pressure gradient between the venae cavae and the right atrium, nor between the pulmonary veins and the left atrium. Consequently, the hemodynamic results of acute cardiac tamponade cannot be ascribed to an obstruction of the caval veins at their site of entry in the pericardium.

The most important result of cardiac tamponade—the decreased cardiac output—is explained by a diminution of the space available for diastolic expansion of the ventricles. It is generally stated that a risk of cardiac standstill exists with a decreasing "effective filling pressure" of the ventricles. The effective filling pressure of the right and left ventricle is obtained by subtracting intrapericardial pressure in late diastole from right and left mean atrial pressure respectively. With the onset of tamponade, the right atrial pressure rises. This is thus the prerequisite for passage of blood to the right ventricle. In severe cardiac tamponade, a decrease in the effective filling pressure of only a few centimetres of water may be detrimental. Certain therapeutic and clinical observations in cardiac tamponade are explained by this fact.

Thus, death not infrequently occurs during induction of anesthesia with positive-pressure respiration, or in connexion with thoracotomy. Here, there is a rise in intrapleural pressure, or cessation of the normal, negative intrapleural pressure, respectively, with a decrease in the effective filling pressure as a result. Blood transfusion has proved to be of value in cardiac tamponade, presumably due to the resulting rise in venous pressure and right atrial pressure, and thus in the effective filling pressure. Aspiration of a mere 10–15 ml of fluid from the pericardium may suffice to produce immediate improvement in the patient's condition.

SYMPTOMATOLOGY AND DIAGNOSIS

The symptoms and signs of acute cardiac tamponade have long been known. Typical precordial pain is present in some cases, but is lacking in others. The patient is usually anxious and restless; dyspnea and cyanosis often occur, as well as coldness of the extremities. The pulse is rapid, soft and hard to palpate. The blood pressure may be low or not measurable. The peripheral veins are engorged, as a sign of congestion. The symptoms may, however, be insidious, at any rate initially.

By what means then can the diagnosis be established before onset of the dramatic final stage? Inspection will disclose any external signs of a penetrating wound, for example. The signs may be inappreciable or absent, e.g. after blunt violence. Engorged, distended veins argue in favour of a diagnosis of cardiac tamponade, and an approximate idea of the pressure in an arm vein can easily be obtained. Determination of the venous pressure is, in fact, a simple procedure and, as described earlier, gives a conception of the pressure conditions in the

and cardiac tamponade, as well as the risk of secondary thrombosis. Moreover, there was a risk of the foreign body becoming detached from the wall, and adhering to some other, equally unsuitable structure. At operation, the pericardium was found to be greatly distended. It was incised, and 170 ml of pure blood were aspirated. The piece of wire, about 1.5 cm long, was found in the wall of the right atrium, just below the opening of the superior vena cava. After removing it, the wall was sutured to arrest the hemorrhage. A small hematoma was also present in the aortic wall, slightly above the sinus of Valsalva, evidently where the foreign body had impinged on the aorta. The postoperative course was uneventful.

ETIOLOGY

The most common injuries to the heart are penetrating knife wounds and gunshot wounds. As a rule, these wounds are localized to the right or left ventricle, and somewhat less often to the right atrium. The left atrium, on the other hand, is seldom involved, in view of the better protection afforded by its more posterior position. Occasional cases have been reported in which the wound has been confined to the coronary artery or one of its branches, the myocardium thus being otherwise undamaged.

PATHOPHYSIOLOGY

Cardiac tamponade is the most serious consequence of a heart wound. Under ordinary conditions, diastolic filling of the heart takes place passively. Even very slight external pressure suffices to form an impediment to filling. External pressure may be due to transudate, exudate, blood or gas in the pericardium. When filling of the pericardium occurs rapidly, an inappreciable quantity of fluid (150–300 ml) may be life-threatening, since the parietal pericardium does not have time to distend. The elasticity of the pericardium allows only limited distension. This has been confirmed by experimental studies on the pressure-volume curves of the pericardium (Isaacs, Berglund & Sarnoff, 1954). Thus, in experiments on dogs, an increase in volume of the pericardium initially produced only an insignificant rise in pressure. A successive increase in volume, on the contrary, soon resulted in a rapid rise in intrapericardial pressure (Fig. 1). This does not apply to chronic distension, as in chronic pericarditis, when one litre of fluid or more may be present in the pericardium without signs of tamponade (Royster & Bosher, 1958).

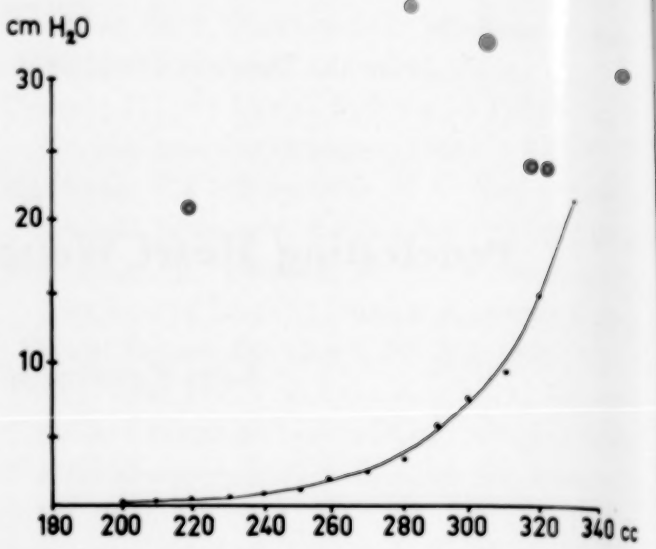


FIG. 1. Pressure volume curve of pericardium, from Isaacs, Berglund & Sarnoff, *Am. Heart J.*, *48*: 66, 1954. Dog experiment. At the lower part of the pericardial curve, substantial increases in volume are associated with only small pressure rises. When the pericardium is further distended (with fluid or air), even a small increase in volume produces a large increase in pressure.

Various explanations have been given of the hemodynamic changes in acute cardiac tamponade. As early as 1882, Cohnheim put forward the theory that

administration of fluid with constant supervision of the patient is, however, generally considered as suitable. If there is clinical improvement, with a rise in arterial pressure and only moderately raised venous pressure, transfusion is of value. In some cases, dramatic and definite improvement has been brought about by this means alone (Blalock & Ravitch). Aspiration is then performed as soon as the diagnosis has been made, or even immediately, to establish it.

Most surgeons perform pericardiocentesis by inserting the needle immediately to the left of the base of the xiphoid process, after which the needle is directed obliquely upwards. If blood that does not coagulate is withdrawn, it is assumed to have come from the pericardium; if the blood coagulates, it is probable that the needle has entered one of the chambers of the heart. Aspiration, often of a surprisingly small quantity of fluid, results in dramatic improvement. The patient is then kept under close observation. If necessary, aspiration is repeated. Should the symptoms nevertheless reappear rapidly, e.g. within half an hour, immediate operation is considered to be indicated.

DISCUSSION

Operation was performed on both our patients, owing to the presence of a foreign body in the pericardium and atrial wall, respectively, with associated hemopericardium. In both cases the patient was evidently on the verge of acute cardiac tamponade, although no marked symptoms had yet had time to develop. In cardiac tamponade, the symptoms are, in fact, apt to have a sudden onset. It is therefore of the utmost importance to realize which patients are liable to be threatened by this condition. To this category belong patients who have suffered a penetrating wound or blunt blow in the heart region. But the risk also exists after interventions on the heart, either open or closed, and after direct puncture for diagnostic purposes, perhaps especially of the left ventricle.

These patients must be kept under close supervision, and treatment of eventual tamponade should be well planned. The arterial and venous pressure should be determined. (Valsalva's test will temporarily accentuate the symptoms.) Fluoroscopic observation of absence or decrease of pulsations is an extremely important and early sign. Obviously, pericardiocentesis is another diagnostic possibility.

When cardiac tamponade appears, there is no time for delay, but one must be prepared to intervene immediately. As stated earlier, it seems to be generally agreed that treatment should consist in the first place of aspiration of the increased fluid content of the pericardium. Symptoms of cardiac tamponade may disappear after removal of only a small quantity of fluid. It must, however, be borne in mind that the patient is still close to the borderline of acute tamponade, and therefore requires continued, careful observation. Several cases have been reported in which the patient was sent home, evidently with a certain quantity of fluid in the pericardium, although he was asymptomatic; a fresh hemorrhage or increase in the exudate

right atrium. High venous pressure suggests cardiac tamponade, but its existence is not ruled out by normal pressure. This may instead be an indication of decreasing effective filling pressure in the ventricles, and thus be an exceedingly unfavourable prognostic sign (Elkin, 1944, 1951). Falling arterial pressure with decreasing pulse pressure strongly supports a diagnosis of cardiac tamponade.

In pericardial effusion, as in hemopericardium, the ECG shows elevation of the ST segment in all three leads. Compression and ischemia of the subendocardial muscle layer are considered to be responsible for these changes. Arrhythmias and block of varying degree may also be observed. Some authors attach great importance to the appearance of the ECG (e.g. Blalock & Ravitch, 1943), whereas others regard the changes as being of less value for early diagnosis (Elkin & Campbell, 1951). The consensus of opinion nevertheless seems to be that repeated ECG control may be of value in cases under observation for suspected tamponade, and as a check-up after removal of blood from the pericardium, either surgically or after pericardiocentesis.

Roentgenologic examination is not considered to be of any great diagnostic value in acute cardiac tamponade. The enlargement of the heart may be due to dilatation, pericardial exudate or both (Krook, 1954).

Fluoroscopy—which shows the absence of pulsations or their decrease—is, on the contrary, always a particularly valuable diagnostic tool in the early stage of cardiac tamponade. This has been pointed out by most authors (e.g. Elkin; Tearse, 1957), and is in good agreement with our experience.

TREATMENT

It is natural that, since the earliest times, injuries to the heart have been regarded as particularly serious. According to Elkin (1951) Cabriolanus was, however, able to show as early as 1604 that heart wounds are not necessarily fatal. Riolanus understood the value of aspiration, and suggested this procedure in 1649. Larrey seems, however, to have been the first to carry out this intervention in 1829. The first successful cardiorrhaphy was performed in 1896 by Rehn.

In recent years, there has been a tendency to apply increasingly conservative therapy. Elkin's views on this question are illustrative. Thus, in a survey of treated cases in 1941, operation is stated to be indicated as soon as the diagnosis has been made. In 1944, some form of conservative treatment is suggested "if conditions are not urgent and operation does not seem to be immediately demanded". In 1951, he recommends conservative treatment as a primary measure in every case. The same opinion has been expressed by most authors who have dealt with these problems (Blalock & Ravitch; Cooley *et al.*; Royster & Bosher; Sawyer *et al.*; Tearse; Wiklund).

The treatment recommended is largely as follows. On admission, blood transfusion is given or, while awaiting it, glucose intravenously. Some authors are more sceptical regarding an increase in blood volume (Sawyer *et al.*). Cautious i.v.

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The Differential Pressure in Aortic Valvular Stenosis

A Theoretical and Diagnostic Study

I. G. PORJÉ and B. RUDEWALD

INTRODUCTION

In earlier works the hemodynamics of aortic valvular stenosis with special regard to the jet-effect has been studied (Castenfors, Porjé & Rudewald, 1954; Porjé & Rudewald, 1957). In these works we have pointed out that immediately distal to the stenosis the lateral pressure is decreased, and it varies at different points of the cross-section with a pressure minimum at the centre. This reduction of the pressure is thought to lower the coronary flow especially during systole. The cause of pulsus tardus does not seem to be the stenosis in itself but a change in the pumping action of the heart (Castenfors, Porjé & Rudewald, 1954). We also studied the pressure gradient across the stenosis. The present work deals with differential pressures and absolute pressures only distal to the stenosis.

In 1957 Porjé & Rudewald reported the first differential pressure recordings from the human aorta. In cases with aortic stenosis we noticed that the shape of the differential pressure curve was quite different from that obtained in normal cases. By improving the frequency properties of the recording apparatus we can now record the differential pressure in the aorta through a rather thin double lumina catheter. Further investigations in cases with aortic valvular stenosis show that just above the valves we get typical differential pressure curves (Δp curves) and the contour of the curves is altered in a characteristical manner when the Δp curve is recorded at increasing distance from the valves. The theoretical and diagnostic significance of these observations are studied here in a special circulation model with experimentally developed stenosis.

MODEL EXPERIMENTS

The experimental arrangement is shown in Fig. 1. The output characteristics of the pump are the following: Stroke volume, 66 cm^3; duration of pump cycle, 0.82 sec.; duration of systole, 0.33 sec. The circulating liquid is water at 18°C.

A double lumina catheter (outer dia-

occurred, resulting in acute cardiac tamponade and sudden death. Consequently, it might be advisable to widen the indications for exploratory thoracotomy in borderline cases.

Aspiration should be carried out before every pericardiotomy on the indication of existing or threatening cardiac tamponade. This is in order to prevent an acute rise in intrapericardial pressure in connexion with induction of anesthesia and thoractomy, respectively. For the same reason, artificial respiration with alternating positive and negative pressure is preferable to positive-pressure respiration only.

SUMMARY

An account is given of two cases of a foreign body in the pericardium and right atrial wall, respectively, and an increased amount of fluid in the pericardium. The physiology and symptomatology of acute cardiac tamponade, as well as the diagnostic possibilities available for detecting the condition in time, are discussed against this background. It is recalled that the pathophysiologic features consist of a rise in intrapericardial pressure, accompanied by a rise in atrial pressure, in order to maintain the effective filling pressure of the ventricles. There is also a rise in pressure in the systemic and pulmonary veins, as well as falling pressure in the systemic arteries and a decrease in cardiac output. Fluoroscopy shows a quiet heart, venous pressure measurements raised pressure, and the ECG signs of pericarditis. Therapy should consist in the first place of aspiration of the fluid, but pericardiotomy should be undertaken in doubtful cases.

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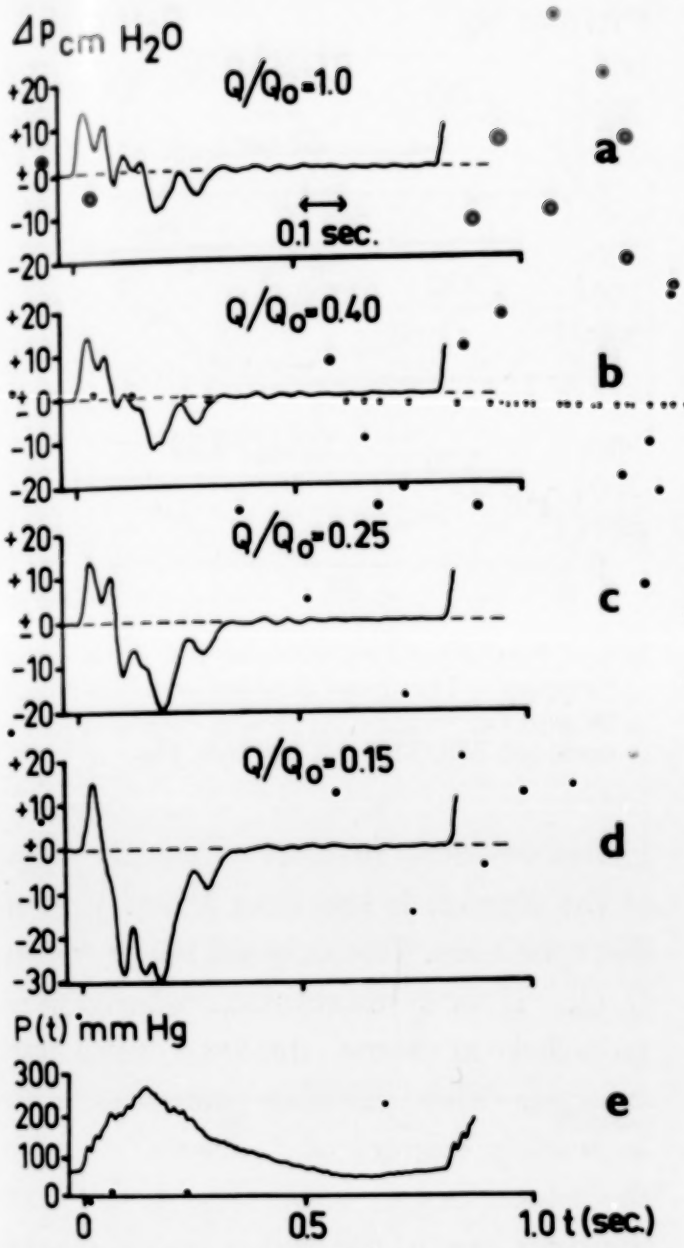


FIG. 4. Redrawn differential pressure curves from the circulation model with varying degrees of "stenosis" (*a–d*). Bottom curve (*e*) is the pressure 15 cm from the "stenosis."

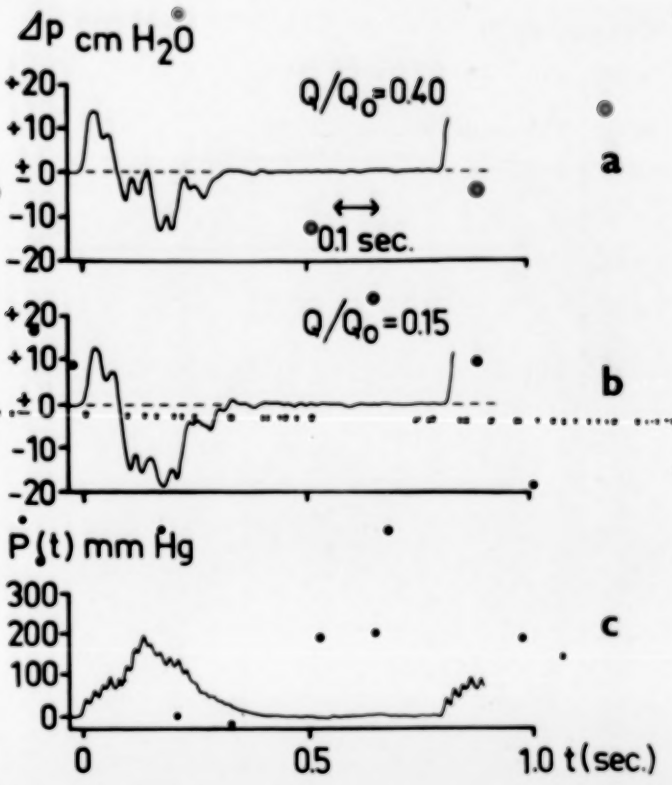


FIG. 5. Differential pressure curves from two different degrees of "stenosis" (*a*, *b*) with low static pressure level in the circulation model. Bottom curve (*c*) is the pressure 15 cm from the "stenosis".

differential pressure. Fig. 4*a* shows the Δp curve with $Q/Q_0 = 1$, i.e. no "stenosis". With increasing degrees of "stenosis" the shape of the Δp curve is changed in accordance to Fig. 4*b*, *c*, and *d*. The characteristical feature of this change is an increasing negativity starting from the late part of the systole and the mean Δp is negative. This change is clearly detectable only when Q/Q_0 is less than about 0.4 and for lower values of Q/Q_0 it becomes very pronounced. The Δp curve returns to zero level at the end of the ejection phase except for high degrees of "stenosis" where a very slight negativity is noticed. The shape of the pressure curve (Fig. 4*e*) at 15 cm from the "stenosis" is unchanged during the experiment.

By changing the static pressure niveau in the circulation system, pressure curves of somewhat different appearance are obtained. The stroke volume of the pump and its output characteristics are unchanged. The Δp curves from varying degrees of "stenosis" are fundamentally the same (Fig. 5*a* and *b*) as above.

We now fix the area quotient at 0.3 and restore the static pressure in the circulation system to its original niveau. The Δp curve is recorded (Fig. 6*a*) and

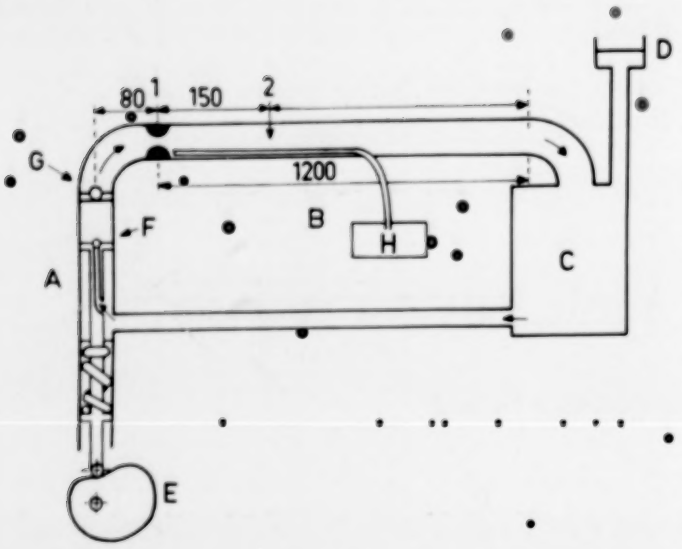


FIG. 1. Diagram of the circulation model. The output characteristics of the pump (A) are determined by the shape of the excentric (E). The liquid is pumped through an elastic tube (B) 1200 mm long and different degrees of "stenosis" are produced at the central end of the tube (*1*). A double lumina catheter is introduced into the tube and attached to the differential pressure transducer (H). For further details see Castenfors, Porje & Rudewald (1954) and Porjé & Rudewald (1957).

meter 2.5 mm) is introduced into the elastic tube. The position of the catheter in relation to the "stenosis" is shown in Fig. 2. Through this catheter the differential pressure between two points at a fixed distance of 10 cm ($L = 10$ cm) is recorded. The frequency properties of the recording system (Fig. 3) are such that pressures up to 14 cycles/sec can be

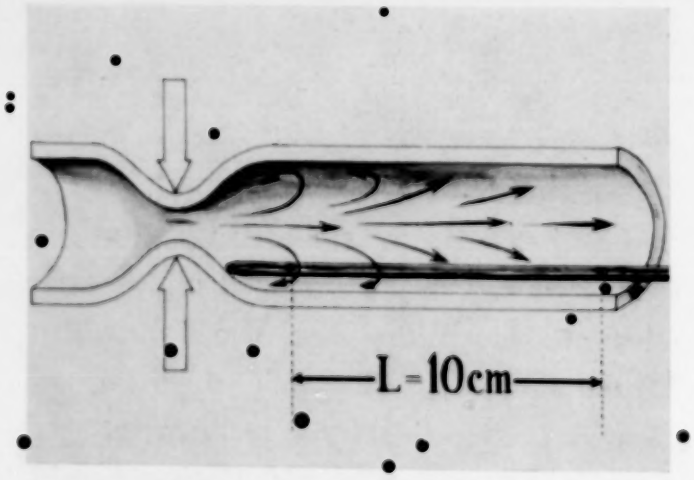


FIG. 2. Diagram of "stenosis" and double lumina catheter and the approximate relation of the jet direction to the position of the catheter.

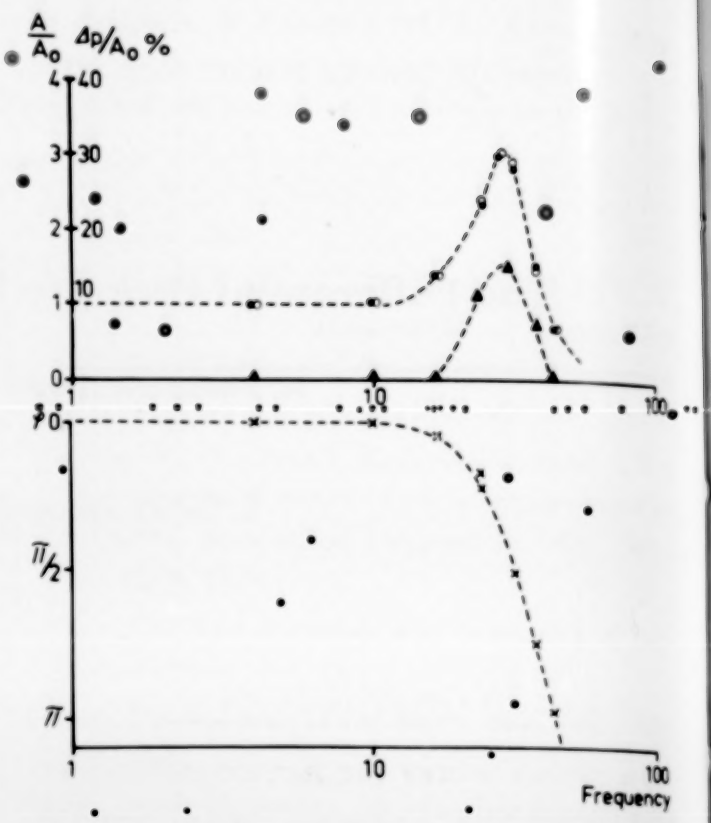


FIG. 3. Dynamic properties of the differential pressure transducer and 100 cm long double lumina catheter. Upper diagram shows the amplitude response (A/A_0) as a function of frequency for both sides of the pressure transducer (● and ○). Solid triangles (▲) represent the dynamic imbalance of the system. Lower diagram shows the phase lag for different frequencies.

recorded with flat response and no phase lag. Higher frequencies are electrically filtered off. At the central end of the tube (Fig. 1: *1*) varying degrees of "stenosis" are produced by outer clamps on the tube. The degree of "stenosis" is expressed by the area quotient Q/Q_0, where Q is the area of the "stenosis" and Q_0 the area of the tube. Thus increasing degrees of "stenosis" means decreasing values of the area quotient.

The experiments are started by recording the Δp curve with the catheter in the position shown in Fig. 2. The pressure 15 cm distal to the "stenosis" (Fig. 1: *2*) is recorded synchronously with the

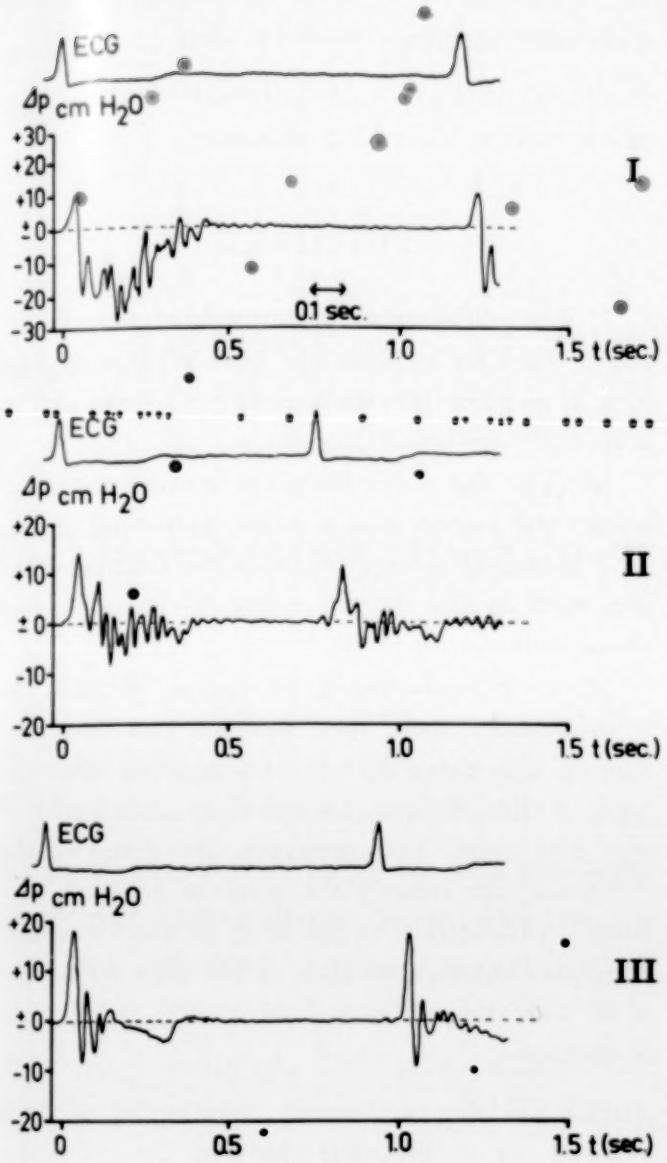


FIG. 8. 49-year-old woman with aortic valvular stenosis. Differential pressure recorded from different positions (I, II and III in Fig. 9) in the aorta. See text.

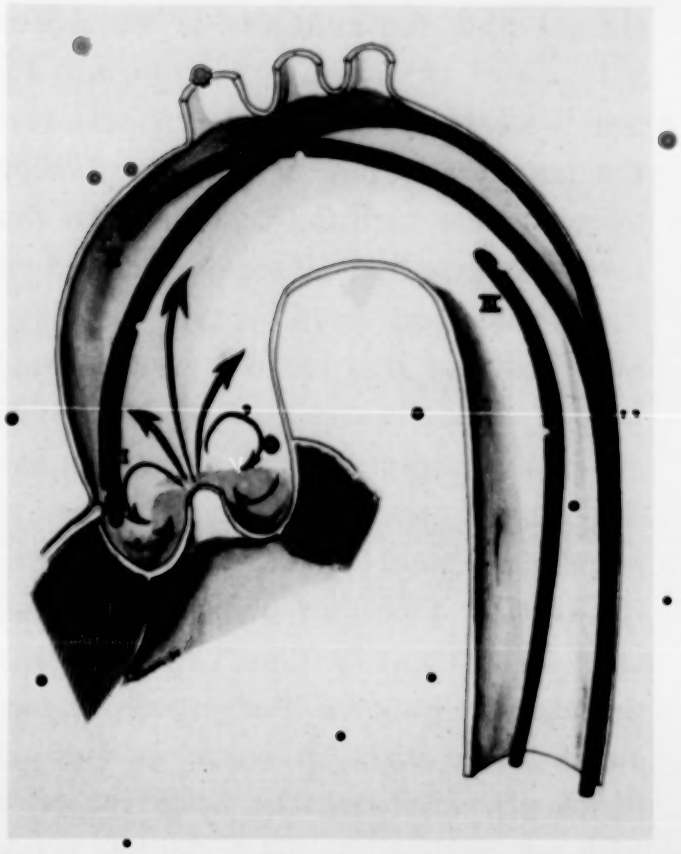


FIG. 9. The approximate position of the double lumina catheter in the aorta. Differential pressure curves from positions corresponding to I, II and III are shown in Fig. 8.

demonstrated in Fig. 8. The Δp curve is recorded with the catheter in different positions shown in Fig. 9. The shape of the Δp curves from these positions is of particular interest.

Near the stenosis the Δp curve starts with a short positive peak followed by a strongly negative part during the remaining part of systole. The mean differential pressure is negative. At greater distance from the stenosis we get Δp curves of rather normal shape and the mean Δp is nearly zero.

DISCUSSION

The characteristic features of Δp curves obtained just distal to the stenosis are due to the fact that there is a central decrease of the lateral pressure within and around the jet from the stenosis, while the pressure at some distance from it, where the jet-effect is reduced, is higher or nearly the same as without stenosis. By withdrawing the catheter it is possible to get Δp curves of rather normal shape.

The position of the catheter in the vessel will influence the Δp records because the pressure distribution is not uniform over the cross-section. The lateral pressure is lowest within the jet and it depends on the fluid velocity. Other factors such as the direction of

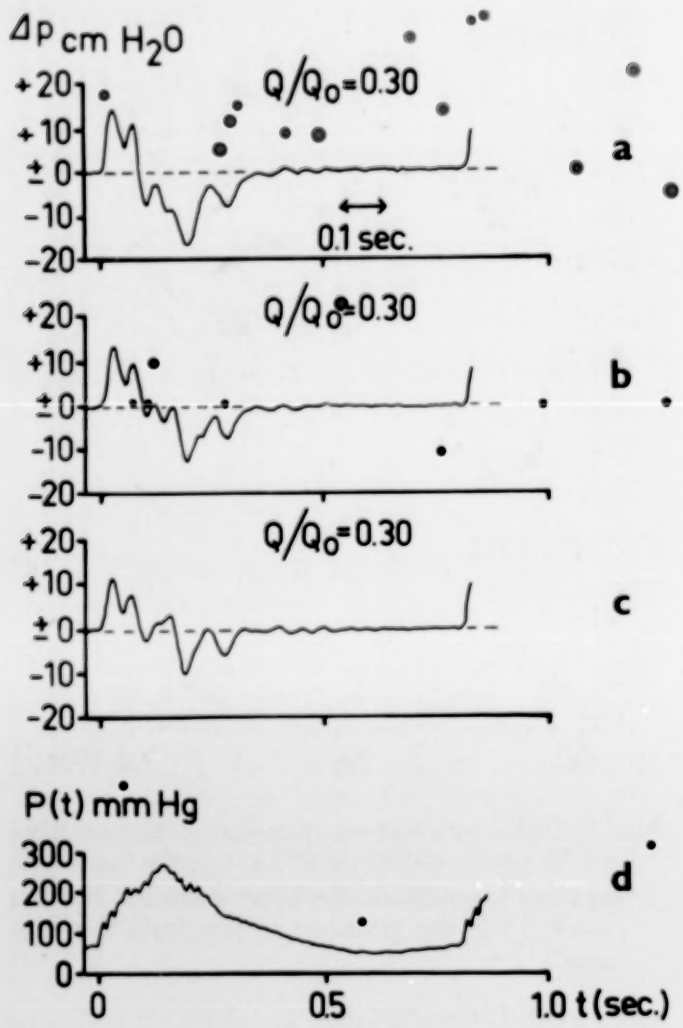


FIG. 6. Top curve (*a*) is recorded just distal to the "stenosis", (*b*) with the tip of the catheter about 5 cm from the "stenosis", and (*c*) 11 cm from the "stenosis". See text.

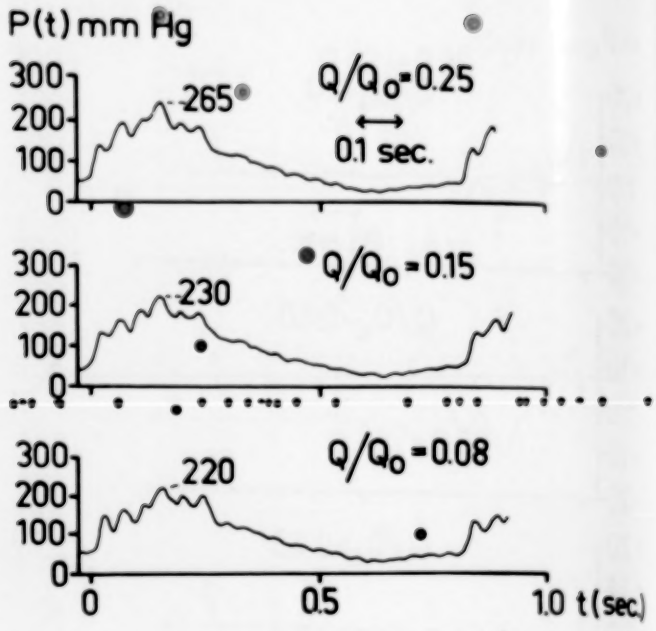


FIG. 7. Pressure curves recorded just distal to the "stenosis". The mean pressures are 110, 96 and 90 mm Hg and corresponding maximum pressures are 265, 230 and 220 mm Hg.

then the catheter is withdrawn. The Δp curve gradually returns to its original shape (Fig. 6*b* and *c*) which occurs at a distance from the "stenosis", that varies with the degree of "stenosis".

Pressure recordings from a point about 2 cm distal to the "stenosis" and near the wall of the tube (Fig. 2) show that maximum pressure and mean pressure are practically unchanged when the area of the "stenosis" is greater than about 20 % of the tube area (Fig. 7). Our observations from these model experiments can be summarized thus:

(1) *The Differential Pressure Curves* just distal to the "stenosis" are changed in a characteristical manner when the area of the stenosis is less than about 40 % of the tube area. The original shape (when $Q/Q_0 = 1$) is re-established when Δp is recorded at some distance from the stenosis. This distance increases with increasing degrees of "stenosis". Under the experimental conditions given here the Δp is zero at the end of systole except for very high degrees of "stenosis" when a very slight negativity is noticed.

(2) *The Pressure Curve* just distal to the "stenosis" (Fig. 2) is mainly unchanged when the area of the "stenosis" is greater than about 20 % of the tube area and higher degrees of "stenosis" cause a reduction of maximum and mean pressure. Recordings from points more distal to the "stenosis" are mainly unchanged at varying degrees of "stenosis".

Aortic Valvular Stenosis

The Δp curve from the aorta has been recorded in three cases with aortic valvular stenosis. One of them is

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Treatment of Patients with Mitral Valvular Disease by Radioactive Iodine

HARALD ELIASCH, HÄRJE BUCHT, LARS-G. LARSSON, BÖRJE RUDEWALD, BENGT THOMASSON, EDVARD VARNAUSKAS and LARS WERKÖ.

The palliative treatment of cardiovascular disorders such as angina pectoris and congestive heart failure by ablation of the thyroid gland either using thiouracil compounds (Raab, 1945; Frisk & Lindgren, 1948) or radioactive iodine (Blumgart, Freedberg & Kurland, 1950, 1951, 1955; Blumgart & Freedberg, 1952; Jaffe, Rosenfeld, Pobirs & Stuppy, 1953, 1955; Chapman, 1958) has yielded promising results. In the late nineteen-forties surgical treatment for mitral stenosis was reintroduced and evidence of the beneficial effect of valvulotomy in many patients was soon presented. Yet it became evident that, for some reason or other, certain patients did not experience relief of symptoms after surgery, and that the operative risk was too high for others. As conservative treatment in these patients failed to alleviate progression of symptoms they were regarded as suitable for treatment with radioactive iodine.

This paper reports the effect of radioactive iodine on a selected group of twenty-four patients with mitral valvular disease. Only those patients who were submitted to right heart catheterization before treatment and where the time of observation was at least five years were included. In some patients right heart catheterization was repeated after the treatment.

MATERIAL

Twenty-four in-patients (St. Eriks Hospital) with mitral valvular disease were studied. There was no clinical evidence of other valvular lesions. None showed signs of either thyreotoxicosis or hypothyroidism. In patient No. 511 a toxic nodular goiter had been removed 1½ years before the first study.

All except one were females. The age ranged between 35 and 63 years of age. Four had sinus rhythm, one atrial flutter and the remaining nineteen atrial fibrillation.

The patients were grouped clinically according to the criteria of the New

the jet and the anatomy of the aortic valves and the aorta are important for the pressure distribution. Furthermore, the catheter is not in a fixed position owing to the high fluid velocity. In this complex situation it seems justified to state that Δp curves of the type described here indicate that there is an abnormal hemodynamic situation in the aorta, generally characterized by negative mean differential pressure. As to the pressure records, we note from our model experiments that a certain degree of stenosis can be present without causing any detectable change of the central pressure curve while the Δp curve is characteristically changed. As Δp is recorded with more than ten times higher sensitivity than the pressure it is obvious that much smaller deviations from a normal pattern can be detected. We think that this fact should be valuable for the differential diagnosis in aortic valvular diseases.

As shown in model experiments, the duration of systole can be determined from the Δp curve with good accuracy. It seems reasonable to assume that we can apply this to the Δp curves from the human aorta even in cases with aortic valvular stenosis.

The results presented here indicate that the recording of differential pressure near the stenosis and at different distances from it offers distinct possibilities to analyse the hemodynamics of aortic valvular stenosis and it also seems possible to improve the diagnosis in cases with aortic valvular diseases.

SUMMARY

1. The differential pressure (Δp) distal to an aortic valvular stenosis has been studied in man and in an experimentally produced "stenosis" in a special circulation model.

(*a*) The Δp curve from the human aorta just above the valves has a quite abnormal shape. The mean Δp is negative. At some distance from the stenosis the Δp curve has a rather normal shape and the mean Δp is nearly zero.

(*b*) In experimentally produced "stenosis" in a circulation model these features can be reproduced. The mean Δp becomes negative when the area of the "stenosis" is less than about 40 % of the tube area. The pressures just distal to the "stenosis" are mainly the same as without "stenosis", provided that the area of the "stenosis" is greater than about 20 % of the tube area.

2. The theoretical and diagnostic significance is discussed.

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TABLE 1. Radioiodine and thyroid function in 24 patients with mitral valvular disease.

Observations were made before and after the administration of radioactive iodine. (*a*) Alive patients. (*b*) Dead patients. Signs of hypothyroidism: o = none; (+) = slight; + = moderate; + + = permanent.

Case No.	I^{131} treatment: Time after 1st I^{131} therapy, months	I^{131} treatment: Dose, mC	I^{131} tracer, 24 hours uptake per cent: Before	After 1–3 months	After 4–6 months	After 7–12 months	BMR, per cent: Before	Min. value	When last exam.	Cholesterol, mg per cent: Before	Max. value	When last exam.	Clinical signs of hypothyroidism	Subst. therapy started after last I^{131} dose, months
(a) Alive patients														
155		6	71	71			+12	+11		248	304		0	—
	3	8	71	47	45	46	+11	−10		304	316		0	—
	32	6	53	—	36	42	−10	+11	+35	222	238	238	(+)	—
302		6	—	—	—	—	+14	−16		210	495		0	—
	30	20	34	4			+24	−18	+25	372	490	284	+ +	4
324		15	24	8	27	—	±0	−27	—	290	271	—	+ +	—
339		6	41	—	—	—	±0	−17		300	309		0	—
	12	8	34	18	11	12	−11	−38	−24	255	345	345	+ +	48
359		6	62	22	38		+21	+12		256	455		0	—
	4	8	38	5	32	11	+12	+1		243	305		(+)	—
	14	33	11	2			+1	−5	−5	305	455	293	+ +	4
385		7	43	5	—	11	−6	−12	−12	165	210	210	+ +	—
410		7	34	16	—	25	+2	−16	−14	270	301	228	+ +	52
432		8	63	17	10	6	+23	−18	−2	233	526	324	+ +	9
485		7	47	13	26	24	+21	−10	−10	—	310	199	+ +	20
495		10	17	30	—	22	−3	−23	−7	298	350	350	+ +	—
511		6	52	18	16	18	+25	−6	−6	330	520	462	+ +	19
616		5	58	30	27		−1	±0		240	350		0	—
	7	20	27	11	—	14	+1	−16	−9	350	437	437	+ +	—
620		25	34	6	9		+17	−20	−2	266	596	440	+ +	6
657		8	27	42			+21	+22		192	383		0	—
	2	25	42	15	9	24	+22	−7	+10	383	504	250	+ +	12
733		25	34	4			+35	−3	+15	244	420	230	+ +	3
(b) Dead patients														
180		8	28	4	6	14	+48	−5	+27	169	498	203	+ +	11
409		8	31	5	22	29	+4	−24	−2	187	506	256	+ +	11
475		8	36	21	44	45	+24	+9		220	319		0	—
	11	6	45	—	—	—	+9	—		262	362		no information	
493		7	45	11	11		+7	—	—	210	—	—	+ +	6
526		6	56	32	31	23	+10	+42	—	218	212	—	0	—
	21	25	47	15	—	28	+42	—	—	212	242	—	(+)	—
529		7	40	28	—	37	+18	+9	—	225	225	—	+	—
542		8	30	6	19	32	+27	+10	+15	—	304	278	(+)	—
597		6	55	30	—	47	±0	+10		311	300		0	—
	8	20	47	5			+10	+4	—	300	497	—	+ +	4
617		20	37	5			+3	−3	+2	269	250	194	+ +	6

York Heart Association (1945). Clinical signs of moderate congestive heart failure were present in four (Nos. 180, 409, 542 and 617). A history of arterial embolism was apparent in patient No. 324. Attacks of tachycardia associated with dyspnoea were complained of by the majority of patients, especially by patient No. 339.

Patients selected for treatment with radioiodine were mostly those with progression of symptoms, being over 45 years of age, having atrial fibrillation and relatively gross enlargement of the heart size.

Most patients received digitalis preparations before radioactive iodine treatment. As a rule the amount required after this treatment was considerably smaller. Chlorothiazide, 250 to 500 mg daily together with one to three grams of potassium chloride, was administered to most patients during the past 1½ years.

METHODS

Right heart catheterization according to Cournand (1947) was performed in all patients before treatment. The studies were made in the recumbent position and in the postabsorptive state. 0.2 g of sodium amytal was given two hours before the investigation. The catheter was introduced into a medial cubital vein and the tip advanced via the pulmonary artery to the wedged position in the periphery of the lung (Lagerlöf & Werkö, 1949). The catheter was then withdrawn and left in the main stem of the pulmonary artery. An indwelling needle was placed in the brachial artery.

After 30 minutes of rest, measurements of pressure, using the strain gauge, and of cardiac output, using the Fick principle, were made.

Right heart catheterization was performed again after treatment in nine patients. In some, the same procedure as above was adopted while in others the catheter was introduced percutaneously into the right femoral vein, leaving the tip in the right ventricle. Pressures were measured and the cardiac output determined, using a right ventricular sample for mixed venous blood.

The heart volume was estimated roentgenologically after the method of Liljestrand, Lysholm, Nylin & Zachrison (1939).

The method of radioiodine tracer studies was described before by Larsson & Ragnhult (1953).

RADIOIODINE TREATMENT AND THYROID FUNCTION

Normal thyroid tissue is relatively radio-resistant. Nevertheless it is almost always possible to induce myxedema by radioiodine administration providing that sufficiently large doses are given.

Most authors have treated euthyroid cardiac patients with relatively large therapeutic doses (15–30 mC I^{131}) with the purpose of destroying the thyroid gland completely and later reducing the disturbing symptoms of myxedema by a small dose of desiccated thyroid. When the present series was started it was planned to give smaller therapeutic doses (5–8 mC I^{131}) for several reasons. Firstly, doses of this size had not been previously tested in euthyroid subjects. Secondly, it was hoped that it might be possible to obtain an optimal degree of

condition. The daily dose of desiccated thyroid varied between 0.10 and 0.20 mg bound iodine.

In our experience the administration of chlorothiazide was followed by a marked reduction of subjective symptoms caused by myxedema. This is remarkable in as much as the injection of mercurial diuretics rendered no such effect.

RESULTS

The material was separated into two groups, one comprising those fifteen patients who were alive at the end of 1958, and the other nine who had died at that time.

Alive patients (group a)

Clinical data (Table 2 *a*). The age ranged between 35 and 63 years at the

TABLE 2 a. Clinical data in 15 alive patients with mitral valvular disease.

Observations were made before and after the administration of radioactive iodine.

Case No.	Functional group	Sex	Age	Time after I^{131}, years	Rhythm Before	Rhythm After	Heart volume, ml/M^2, BSA Before	Heart volume, ml/M^2, BSA After	Improvement
155	II	F	45	7	S	AF	545	840	yes
302	II	F	48	8	S	AF	650	1060	no
324	III	F	35	6	AF	AF	585	600	no
339	III	M	44	6½	AF1	S	890	1170	yes
359	III	F	43	7	AF	AF	735	700	no
385	III	F	53	7	AF	AF	685	800	yes
410	II	F	59	7	AF	AF	675	610	no
432	IV	F	51	7	AF	S	530	530	yes
485	III	F	63	7	AF	AF	770	1000	yes
495	II	F	45	6½	S	AF	530	610	yes
511	III	F	48	6½	AF	S	610	610	yes
616	III	F	50	6	AF	S	580	660	no
620	III	F	48	6	AF	AF	530	500	yes
657	III	F	55	5½	AF	AF	750	750	yes
733	III	F	51	5	AF	AF	700	810	no

TABLE 2 b. Clinical data in 9 dead patients with mitral valvular disease.

Observations were made before and after the administration of radioactive iodine.

Case No.	Functional group	Sex	Age	Time after I^{131}, years: When last exam.	Time after I^{131}, years: Death	Rhythm Before	Rhythm After	Heart volume ml/M^2, BSA Before	Heart volume ml/M^2, BSA After	Initial improvement
180	IV	F	49	4	4½	AF	AF	720	940	no
409	III	F	46	5	5½	AF	AF	730	1350	no
475	IV	F	51	1½	3	AF	AF	800	1040	no
493	IV	F	52		1	AF	AF	800		no
526	III	F	46	2½	3	AF	AF	600	720	no
529	IV	F	60	½	5	AF	AF	1380	1380	no
542	III	F	43	1½	2½	AF	AF	1380	1360	yes
597	III	F	49	1	2	AF	AF	630	820	yes
617	IV	F	39	5	5	AF	AF	760	1030	yes

permanent hypothyroidism not requiring substitution therapy. Thirdly, the local and general reactions (swelling of the gland, tracheitis, hyperthyroid symptoms) that sometimes occur shortly after large ablation doses of I^{131} might constitute a risk in patients with serious cardiac disease.

All patients in the present series were clinically euthyroid when the treatment started and none of them had palpable enlargement of the thyroid gland. Only one (No. 511) had a history of previous thyroid disease. This patient had a total thyroidectomy for toxic nodular goiter one and a half years earlier but was euthyroid when I^{131} therapy started.

The thyroid function was studied by clinical examination, I^{131} tracer test, BMR and serum cholesterol. Facilities for PBI determinations were not available. The laboratory data are summarized in Table 1. In most patients the radioiodine uptake was within the normal range. A few patients (Nos. 155, 359, 616) had a remarkably high uptake but there was no clinical suspicion of hyperthyroidism. Many patients had before treatment moderately elevated BMR, which, however, is a common observation in cardiac patients.

The therapeutic dose of I^{131} was given orally, usually within one week after the preceding tracer test. When possible, the thyroid function was then studied every second to third month by repeated clinical examinations and laboratory tests. Pertinent data are summarized in Table 1. As regards the tracer tests, only data obtained before the start of substitution therapy were included.

Twenty patients were primarily treated with the small therapeutic dose of I^{131} previously mentioned. In nine this dose was sufficient to induce permanent hypothyroidism. As a rule this state was moderate or slowly progressive and it could also be seen from the tracer tests that the thyroid gland was not completely destroyed. In eleven patients the first dose induced no or only very slight or transient signs of hypothyroidism and eight of these were later on treated again. Three patients were primarily treated with large doses (15–25 mC) and two of them promptly developed myxedema within the first few months while the remainder only showed slowly progressive signs of hypothyroidism.

In the total series, nineteen patients eventually developed permanent clinical hypothyroidism. One patient (No. 475) did not reappear after the last therapy dose and the remaining four had no or only slight signs of hypothyroidism. Also these patients would possibly have developed myxedema after more energetic radioiodine treatment. Two were, however, clinically improved despite the fact that thyroid function was not markedly depressed (Nos. 155 and 542).

Fifteen patients were later treated with thyroid medication, starting from 3 to 52 months after the last therapy dose of I^{131}. Three patients still have an optimal degree of hypothyroidism not requiring substitution therapy. The principle for thyroid medication was to give small doses, sufficient for removal of the most disturbing symptoms of hypothyroidism and for reducing the serum cholesterol to a moderate level without bringing the patient back to an euthyroid

TABLE 3 b. Hemodynamical data in 9 dead patients with mitral valvular disease.

Observations were made during right heart catheterization in the resting state before the administration of radioactive iodine.

Case No.	BSA, M^2	Heart rate, Beats/min.	Oxygen consumption, ml/min.	A – V O_2 diff., ml/L	Cardiac index, L/min./M^2 BSA	Stroke volume, ml/beat	Blood pressures, mm Hg							
							PCV M	PA			RA M	BA		
								S	D	M		S	D	M
180	1.56	88	—	72	—	—	—	128	41	71	10	159	80	104
409	1.61	62	234	63	2.3	60	21	87	48	65	8	200	78	132
475	1.77	91	260	54	2.7	53	21	47	25	32	3	144	98	117
493	1.60	58	158	35	2.8	78	15	56	27	33	2	139	91	112
526	1.45	90	156	64	1.7	27	20	58	29	38	5	113	62	84
529	1.58	68	175	66	1.6	38	25	97	35	50	2	163	93	115
542	1.54	74	178	87	1.3	28	17	75	46	58	8	110	47	73
597	1.63	85	228	54	2.6	50	17	39	21	27	1	165	106	127
617	1.54	95	224	84	1.7	28	22	135	64	102	13	147	83	101

area in five and less in the remaining five patients. In this group six patients felt improved. This could not be correlated to any specific hemodynamic pattern.

In six patients right heart catheterization was performed once or twice after treatment (Table 4*a*). The degree of pulmonary hypertension was considerably less in three patients (Nos. 432, 511 and 657). These felt improved after treatment; no major change in heart volume was observed. Right heart pressures were essentially unchanged in patients Nos. 359 and 485; a moderate pressure increase was found in patient No. 733. The cardiac output tended to decrease or remained unaltered following treatment.

Dead patients (group b)

Clinical data (Table 2*b*).—The age ranged between 39 and 60 years at the time when radioiodine was administered. In four patients the clinical incapacity indicated group III, the remaining five belonging to group IV. Six patients had died between three and five years after treatment and three of these had been last seen between 4 and 5 years after.

All patients had atrial fibrillation at all occasions. The heart volume ranged between 600 and 1380 ml per square meter body surface area before and between 720 and 1380 ml after; the volume had increased in the majority of patients.

Three patients claimed to be initially improved; two of these met with a sudden death (patient Nos. 597 and 617).

Hemodynamic data (Tables 3*b* and 4).—Marked degree of pulmonary hypertension was observed in majority of patients, even in association with a cardiac index of 1.7 liters per minute or less in four patients. Those three patients who were alive until four and five years after treatment had a mean pulmonary arterial pressure of 71, 65 and 102 mm Hg respectively (Nos. 180, 409 and 617).

Three patients were catheterized after

TABLE 3 a. Hemodynamical data in 15 alive patients with mitral valvular disease.

Observations were made during right heart catheterization in the resting state before the administration of radioactive iodine.

Case No.	BSA, M^2	Heart rate, beats/min.	Oxygen consumption, ml/min.	A – V O_2 diff., ml/L	Cardiac index, L/min./M^2 BSA	Stroke volume, ml/beat	Blood pressures, mm Hg									
							PCV M	PA			RV		RA M	BA		
								S	D	M	S	D		S	D	M
155	1.62	79	293	39	4.6	95	18	34	16	24	35	5	4	128	70	93
302	1.66	67	179	49	2.2	55	10	20	9	15	—	—	—	—	—	—
324	1.57	85	206	53	2.5	46	18	29	16	21	—	—	—	113	77	91
339	1.99	117	302	49	3.1	53	16	39	18	24	40	0	0	132	97	111
359	1.66	58	200	61	2.0	56	—	27	9	16	—	—	−1	114	75	88
385	1.72	86	208	48	2.5	50	23	48	25	33	—	—	3	110	64	81
410	1.62	88	206	43	2.9	54	20	38	17	26	—	—	—	162	65	106
432	1.58	111	250	68	2.3	33	15	58	33	40	—	—	2	—	—	—
485	1.55	65	180	51	2.3	54	11	43	20	29	45	2	4	150	93	114
495	1.67	74	181	42	2.6	58	6	26	9	14	—	—	3	111	72	88
511	1.88	68	—	68	2.1	58	20	41	22	30	—	—	—	143	86	105
616	1.84	64	272	45	3.3	94	9	30	8	19	—	—	0	119	63	84
620	1.63	82	254	67	2.3	46	10	34	15	25	31	−3	0	—	—	—
657	1.48	85	222	71	2.1	37	22	66	37	46	—	—	0	225	114	163
733	1.76	80	324	75	2.5	54	21	61	24	38	—	—	6	—	—	—

time when radioactive iodine was given. Four patients belonged to group II, ten to group III and one to group IV. The time of observation was from five up to eight years after treatment. Three patients had sinus rhythm, one atrial flutter and the remaining eleven atrial fibrillation. At the time of follow-up study those who had had sinus rhythm before now had atrial fibrillation while in four the rhythm had changed from fibrillation to sinus.

The heart volume, expressed as ml per square meter body surface area, ranged between 530 and 890 ml before and between 530 and 1170 ml after. The volume had increased more than 200 ml in four patients, remaining essentially unaltered in the others. In two of the patients showing increased heart volume, the cardiac rhythm had changed into atrial fibrillation.

Nine patients considered themselves improved. This was not associated with any particular clinical pattern.

Hemodynamic studies (Tables 3*a* and 4).—In five patients the mean pulmonary arterial pressure was 30 mm Hg or more, associated with a high pulmonary capillary venous pressure (PCV) of 15 to 23 mm Hg. In these patients the cardiac output ranged between 2.1 to 2.5 liters per minute per square meter body surface area. Four of these patients felt improved. No major change in the heart volume had occurred in these.

In the remaining ten patients the pulmonary arterial pressure was either normal or moderately elevated; in four of these the pulmonary capillary venous pressure was pathologically elevated. The cardiac output was 2.5 liters or more per square meter body surface

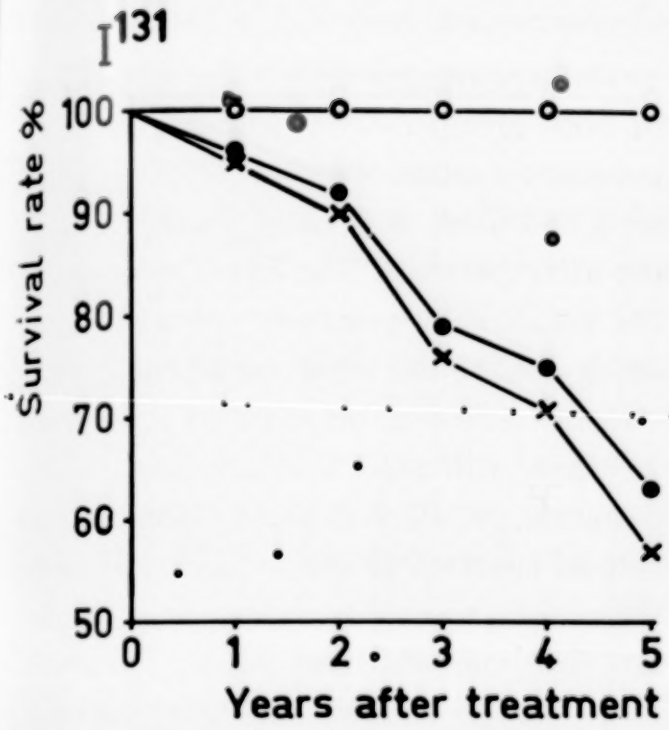


FIG. 1. The influence of the heart rhythm (before treatment) on the survival rate of 24 selected patients with mitral valvular disease who were given radioactive iodine. ●, Total material; ○, sinus; ×, fibrillation.

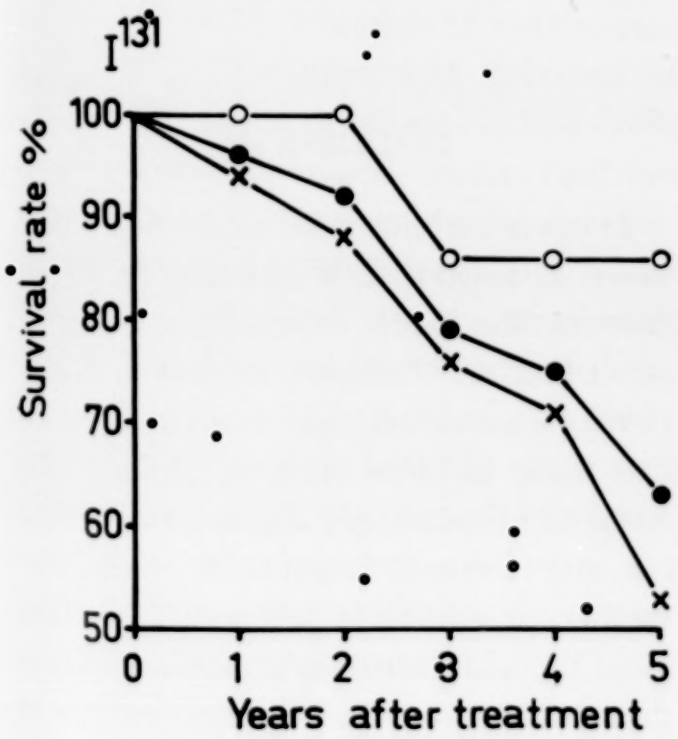


FIG. 2. The influence of the heart volume (before treatment) on the survival rate of 24 selected patients with mitral valvular disease who were given radioactive iodine. The heart volume was estimated by roentgen and expressed as ml per square meter body surface area. ●, Total material; ○, heart vol. ≤600 before treatment; ×, heart vol. >600 before treatment.

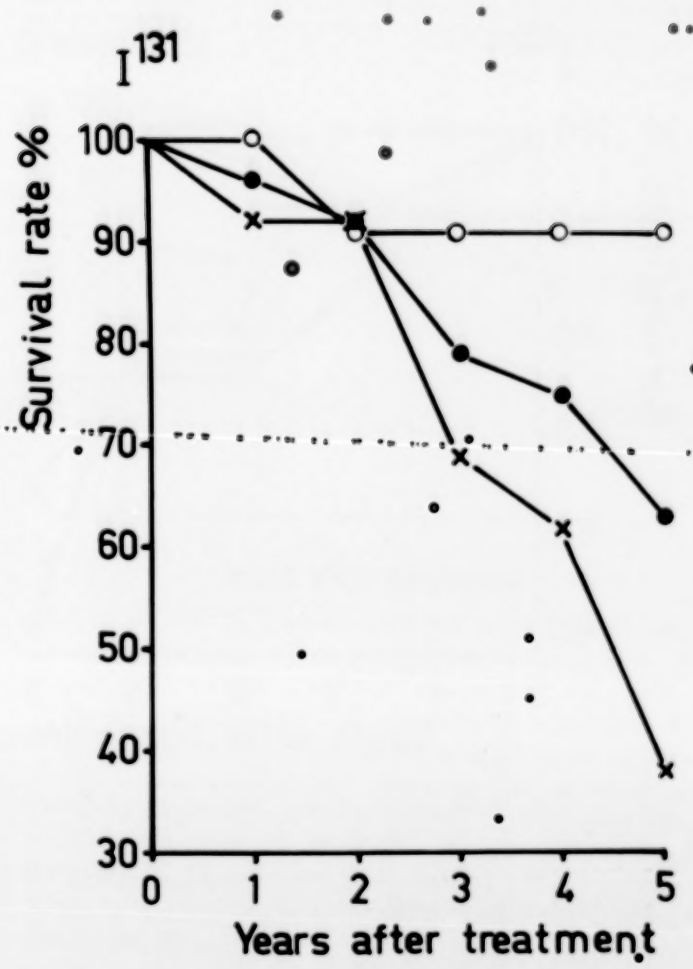


FIG. 3. The influence of the mean pulmonary arterial pressure in mm Hg (before treatment) on the survival rate of 24 selected patients with mitral valvular disease who were given radioactive iodine. ●, Total material; ○, $PA_M < 30$ before treatment; ×, $PA_M \geq 30$ before treatment.

treatment. There was no change in right heart pressure. The cardiac output had decreased in one, increased in the second, remaining unchanged in the third patient.

Cause of death.—Two patients, Nos. 597 and 617, met with sudden death. The remaining patients died from chronic cardiac failure. Autopsy data were available in patients Nos. 180 and 409 showing a narrowed and calcified mitral valve with marked hypertrophy of the right ventricle and gross enlargement of the left auricle. No abnormally increased deposits of cholesterol were found in the arterial vascular system.

TABLE 4. Hemodynamical data in (a) 6 alive and (b) 3 dead patients with mitral valvular disease.

Observations were made during right heart catheterization in the resting state before and on various occasions after the administration of radioactive iodine.

Case No.	Years after treatment	Age	BSA, M^2	Heart vol., ml/M^2 BSA	Rhythm	Heart rate, beats/min.	Oxygen consumption, ml/min.	A – VO_2 diff., ml/L	Cardiac index, L/min. M^2 BSA	Stroke vol., ml/beat	Blood pressures, mm Hg									
											PCV M	PA S	PA D	PA M	RV S	RV D	RA M	BA S	BA D	BA M
(a) Alive patients																				
359		43	1.66	735	AF	58	200	61	2.0	56	—	27	9	16	—	—	−1	114	75	88
1148	7	50	1.77	700	AF	55	210	64	1.9	60	—	—	—	—	21	0	0	125	71	94
432		51	1.58	530	AF	111	250	68	2.3	33	15	58	33	40	—	—	2	—	—	—
671	1½	53	1.70	520	S	89	234	48	2.9	55	11	29	9	19	—	—	0	—	—	—
1149	6½	58	1.66	530	S	79	185	52	2.2	45	—	—	—	—	30	3	0	154	78	106
485		63	1.55	770	AF	65	180	51	2.3	54	11	43	20	29	45	2	4	150	93	114
683	1½	64	1.65	770	AF	77	180	41	2.6	57	12	35	11	19	—	—	3	120	72	93
1151	6½	69	1.61	1000	AF	58	127	52	1.5	42	—	—	—	—	40	8	6	172	86	117
511		48	1.88	610	AF	68	268	68	2.1	58	20	41	22	30	—	—	—	143	86	105
652	1	49	1.98	520	AF	72	228	44	2.6	73	5	24	13	15	—	—	4	164	65	97
1141	6	54	1.98	610	S	57	192	58	1.7	58	—	—	—	—	20	2	1	159	79	106
657		55	1.48	750	AF	85	222	71	2.1	37	22	66	37	46	—	—	0	225	114	163
1136	4½	60	1.50	750	AF	75	155	63	1.7	33	12	28	18	24	29	2	2	190	103	139
733		51	1.76	700	AF	80	324	75	2.5	54	21	61	24	38	—	—	6	—	—	—
1146	4½	55	1.72	810	AF	69	—	45	—	—	—	—	—	—	83	5	6	—	—	—
(b) Dead patients																				
475		51	1.77	800	AF	91	260	54	2.7	46	21	47	25	32	—	—	3	144	98	117
689	1½	52	1.73	1040	AF	114	157	71	1.3	20	—	—	—	30	—	—	6	—	—	96
529		60	1.58	1380	AF	68	175	66	1.6	38	25	97	35	50	—	—	2	163	93	115
623	½	61	1.58	1380	AF	80	232	70	2.1	42	31	116	34	58	128	0	1	95	56	71
617		39	1.54	760	AF	95	224	84	1.7	28	22	135	64	102	—	—	13	147	83	101
1142	4½	44	1.60	760	AF	72	189	66	1.8	40	—	—	—	—	—	—	11	121	70	89

decompensated cardiac patients soon became obvious and the surgical procedure was abandoned. A few years later thiouracil compounds and thereafter, radioactive iodine were introduced for reduction of the thyroid activity and successfully used for relief of cardiac disease (Raab, 1945; Blumgart *et al.*, 1950). The use of radioiodine was preferred because of its ease of administration and the untoward effects that may be encountered with thiouracil preparations.

The effect of radioiodine treatment has so far been studied in euthyroid patients with unspecified cardiac decompensation and angina pectoris while reports of the effect on valvular heart disease have not appeared.

In mitral valvular disease the mechanical hindrance to blood flow may lead to marked reduction of the cardiac output in association with increase in pulmonary blood pressures. If heart rate is abnormally increased, cardiac function will be further impaired due to shortening of the ventricular filling time. It was therefore considered that by producing hypometabolism in these patients the lowered metabolic needs of the body would better comply with the decreased blood flow. Also, slowing of the heart rate would lead to a better filling of the left ventricle thereby reducing the degree of pulmonary congestion.

The present material of patients is fairly small and the end results are inconsistent. The marked reduction of severe pulmonary hypertension associated with definite clinical improvement as observed in some of the patients shows, however, that radioiodine therapy may

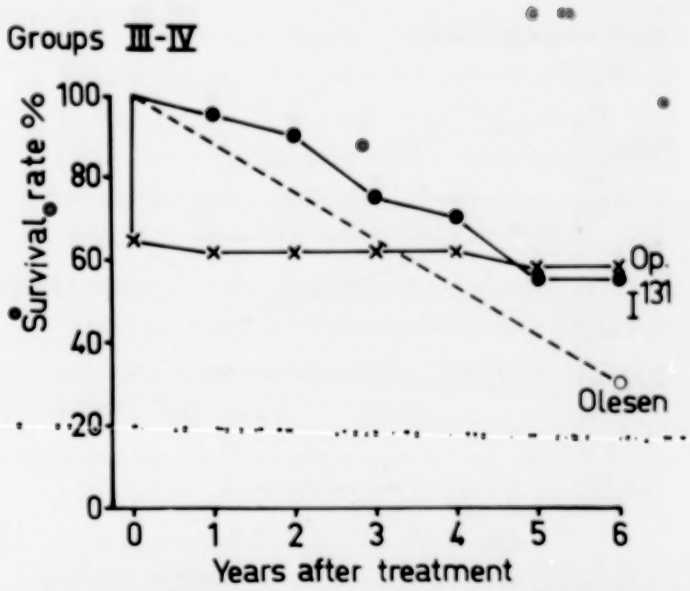


FIG. 6. Survival rate in patients with mitral valvular disease. One group was comprised of patients of the present material; the other group consists of other patients admitted to the same medical service and who were operated upon within the same period of time as radioactive iodine was given. The dotted line represents an estimate of the survival rate of female patients in groups III to IV conventionally treated (Olesen, 1955: mean of survival curves C and D, Fig. 21, page 173). Mean age: ●, 49 ($n=20$); ×, 40 ($n=26$); ○, 45 ($n=112$).

in certain cases yield results equal to those obtained on successful surgery.

The patients belonging to functional groups III and IV were compared with patients of similar clinical incapacity that had been subjected to mitral valve surgery during the same period of time (Fig. 6). The control material was obtained from a follow-up study on patients conventionally treated for mitral stenosis (Olesen, 1955). The different selection of patients in these materials does not justify a direct comparison but it is seen that ablation of the thyroid gland is definitely a therapeutic measure of value. In our experience it serves as an alternative to surgery if operation means a high risk or is refused. Furthermore, it can be used in patients with intractable tachycardia and in those where myocardial insufficiency is a prevalent feature.

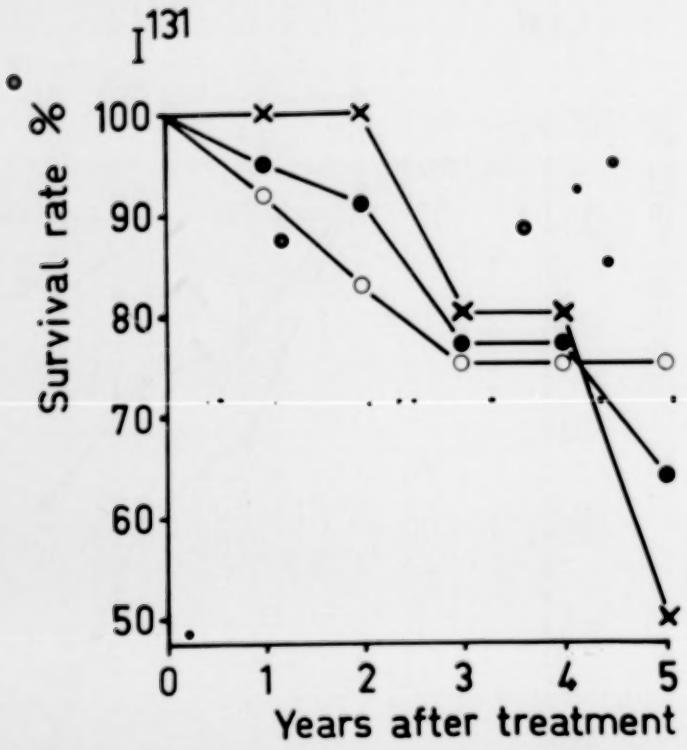


FIG. 4. The influence of the mean pulmonary capillary venous pressure in mm Hg (before treatment) on the survival rate of 24 selected patients with mitral valvular disease who were given radioactive iodine. ●, Total material; ○, $PCV_M \leq 19$; ×, $PCV_M > 19$.

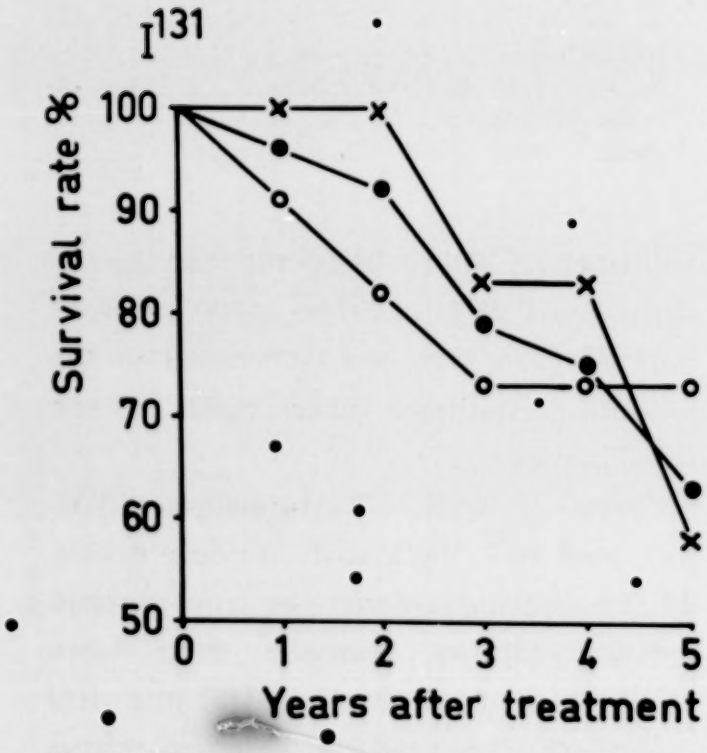


FIG. 5. The influence of the cardiac output (before treatment) on the survival rate of 24 selected patients with mitral valvular disease who were given radioactive iodine. The cardiac output was expressed in litres per minute per square meter body surface area. ●, Total material; ○, C.I. ≥ 2.5 before treatment; ×, C.I. < 2.5 before treatment.

Comparison between groups a and b.

The age ranged within the same limits in both groups. Atrial fibrillation was a constant feature among those patients who had died, and was prevalent among the alive patients. The heart volume and the pulmonary pressures were of higher order among the dead, while the cardiac output tended to decrease in this group.

When different clinical and hemodynamic parameters were related to the rate of survival (Figs. 1–5) it was found that the mortality rate was higher among those who had atrial fibrillation, large heart volume and marked pulmonary hypertension while the level of cardiac output exerted no major influence. Similar findings following surgery for mitral stenosis have been reported before (Werkö, Biörck, Crafoord, Wulff, Krook & Eliasch, 1953).

DISCUSSION

It has been known for many years that there is considerable slowing of blood flow to the body tissues in congestive heart failure. Blumgart, Levine & Berlin (1933) considered that if hypometabolism were induced in such patients the reduced blood supply might be sufficient for the lowered metabolic demands. Earlier promising experience from surgical thyroidectomy in a cardiac patient directed these workers to the concept of producing myxedema in cardiac patients for relief of disease. This was soon confirmed in the reports of Blumgart, Riseman, Davis & Berlin (1933) and of Parsons & Purks (1937). The disadvantage of performing thyroid surgery in

not necessarily associated with reduction in the cardiac output.

5. It is suggested that ablation of the thyroid gland by radioiodine can be a therapeutic measure worth while for relief of mitral valvular disease in those patients where surgery is not advised.

ACKNOWLEDGEMENT

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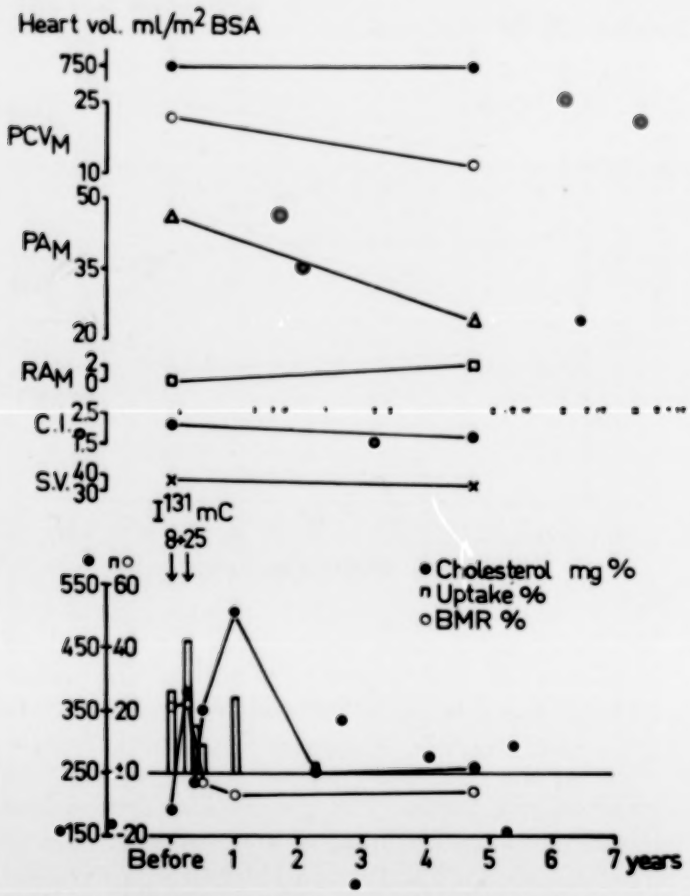


FIG. 7. Clinical and hemodynamical data in a patient with mitral valvular disease (Case 657/1136), before and five years after the administration of radioactive iodine. PCV_M = mean pulmonary capillary venous pressure. PA_M = mean pulmonary arterial pressure, RA_M = mean right atrial pressure. All pressures in mm Hg. C.I. = cardiac output in litres per minute per square meter body surface area. S.V. = stroke volume in ml per beat.

Alleviation of pulmonary arterial hypertension was observed in four patients. In two of these, Nos. 432/671 and 455/683, the pulmonary capillary venous pressure was essentially unchanged while the cardiac output had increased; in other words, there was a marked reduction in pulmonary vascular resistance and only a minor decrease in hindrance to blood flow over the mitral valve orifice. This implies that pulmonary congestion was relieved, probably due to the absence of attacks of tachycardia, so often complained of by these patients. In the third patient, No. 511/652, there was, in addition, a decrease in the pulmonary capillary venous pressure. This finding, otherwise conforming with that observed after successful valvulotomy (Eliasch, 1952), does not necessarily mean that the resistance over the mitral valve had decreased, but may suggest that myocardial failure of the left ventricle was relieved.

In the fourth study, No. 657/1136 the fall in pulmonary arterial and pulmonary capillary venous pressures was probably due to a concomitant decrease in the cardiac output (Fig. 7).

It is thus seen that the hemodynamical consequences of radioiodine treatment may follow different patterns; the lack of uniformity in the response of the cardiovascular system to hypothyroidism has been pointed out by Ellis, Mebane, Maresh, Hultgren & Bloomfield (1952). Although the studies are few it may be said that alleviation of pulmonary congestion was not necessarily a consequence of a decrease in the cardiac output.

SUMMARY

1. Radioactive iodine was given to twenty-four euthyroid patients with mitral valvular disease. Follow-up studies were made at least five years after. Only those patients who before treatment underwent cardiac catheterization, including measurements of pressures and flow in the pulmonary circulation were included.

2. Hypothyroidism was produced in majority of patients; associated symptoms were partially relieved by thyroid substitution therapy and chlorothiazide.

3. There was a gradual fall in the survival rate. Among the fifteen patients who were alive after more than five years the majority claimed to be improved.

4. The hemodynamic response to treatment was studied in nine patients. In four pulmonary arterial hypertension was alleviated which was

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Phonocardiography during Muscular Work in the Evaluation of Mitral Stenosis

GIANNI PINARDI and GUNNAR STRÖM

In mitral stenosis, phonocardiographic recording of the heart sounds at rest may be of value for establishing the diagnosis in certain cases (Kelly, 1955). For example, in rare cases, the opening snap —which is an important diagnostic sign in mitral stenosis (Margolies & Wolferth, 1932; Wolter, 1954; Mounsey, 1953)— may not be audible, although it can be recorded on the phonocardiogram (Mounsey, 1953). In other cases, a presystolic murmur is apparently audible, but phonocardiography shows this auscultatory finding to be due to a crescendo-shaped first sound (Sewall, 1909; Alimurung, 1949) or to a late fourth sound (Johnston, 1935; Bramwell, 1943; Luisada & Montes, 1950).

The greatest diagnostic advantage of phonocardiographic recording is that it offers the possibility of measuring time relations in a quantitative way (Holldack & Wolf, 1956; Sprague, 1954). This advantage can also be utilized in identification of an opening snap (Auinger, 1957; Read & Porter, 1955), and in differentiating it from the pulmonary component of a split second sound (Leatham & Towers, 1951; Leatham, 1954; McKusick, Reagan, Santon & Webb, 1955; Read & Porter, 1955), or from a normal or exaggerated third sound.

Furthermore, it has recently been shown that exact measurement of the time interval between the beginning of the aortic component of the second sound and the opening snap, which has been observed to range from 0.10–0.11 second in moderate mitral stenosis to 0.02–0.05 second in tight stenosis, may provide information about left atrial pressure (Schölmerich & Gehl, 1951; von Bayer, Loogen & Wolter, 1956; Dittrich, 1956; Moret, Schwartz, Arbett, Grossman & Re, 1956; Wells, 1954; Wells, 1957; Wolter 1954)—Fig. 3. The time interval between the R wave of the ECG and the first heart sound is also of value for estimation (Wells, 1954, 1957) of the pressure in this chamber (Fig. 3). The basic assumptions involved in these original measurements have subsequently been studied, and mainly confirmed by direct pressure recordings from the left atrium and ventricle

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increasing intensity (Sjöstrand, 1947; Wahlund, 1948) in the supine or upright body position. Since the construction of a new type of bicycle ergometer (Holmgren & Mattsson, 1954), phonocardiographic recording is technically easier to perform during a work test. Obviously, a recording apparatus of high technical standard is a prerequisite for these studies (Mannheimer, 1940, 1957).

An account is given in the following of phonocardiographic studies at rest and during muscular work in cases of mitral stenosis. Particular interest has been focused on changes in the time interval between the beginning of the second heart sound and the beginning of the opening snap, as well as on certain calculations of left heart function which may tentatively be made on the basis of the phonocardiographic measurements.

CASE MATERIAL AND METHODS

The case material consisted of 27 patients with mitral stenosis, with no or only an inappreciable degree of mitral incompetence apparent; they were examined at the laboratory either to establish the diagnosis, or for preoperative assessment. Catheterization was performed in 21 cases; 13 of these patients were studied at rest only, whereas 8 were studied both at rest and during graded work (Table 1). In addition, 6 patients were studied by phonocardiography at rest and during work, but not by right-heart catheterization. The majority of these patients have also been described elsewhere (Holmgren, Jonsson, Linderholm, Sjöstrand & Ström, 1958).

Phonocardiograms were recorded in the supine body position, usually from the mitral, tricuspid, pulmonary and aortic areas in succession, during voluntary breath-holding at the end of a normal expiration, without occlusion of the glottis and with maximum obtainable muscular relaxation. The patients were carefully controlled so that they did not perform a Valsalva manoeuvre, which had a variable influence on the relevant time interval of second sound-opening snap (2S–OS); after a few heart beats a prolongation was usually seen, as has been pointed out earlier (Wolter, Bayer & Quermann, 1955). This was possible to do even during work, which was performed in the supine position, after the patients had been instructed and trained.

The electrocardiograph "Klinik" (Elema, Stockholm) with phonocardiograph, having one ECG channel (lead I), two channels with differential sound amplification of 25 c/s and 100 c/s nominal frequencies and one channel with auditory amplification (Mannheimer, 1957), was used for recording. An electrically braked bicycle ergometer was used (Holmgren & Mattsson, 1954), which was adjustable for work in the supine position. In a minor proportion of cases the phonocardiograms were recorded during catheterization; in the others, this was not possible for technical reasons and was instead performed one or two days before catheterization, under otherwise identical conditions. Blood pressures were calculated in periods of apnea in the expired lung position. The variation in heart-rate response on the two occasions is apparent from Table 1, where the heart rate both during cathe-

(Blakemore, Schnabel, Kuo, Conn, Langfeld, Heiman & Woske, 1957; Julian & Davies, 1957; Litwak, Samet, Bernstein, Silverman, Turkewitz & Lessler, 1957; Proctor, Walker, Hancock & Abelmann, 1957).

It has long been generally accepted that the opening snap appears at the moment of opening of the mitral valve (Holldack & Wolf, 1956) and this view has also been verified by the aforementioned measurements in heart catheterization studies. Consequently, the time interval from the beginning of the second heart sound to the beginning of the opening snap should, as illustrated by Fig. 3, be dependent on the difference between aortic endsystolic pressure and left atrial endsystolic pressure on the one hand, and on the time course of isometric relaxation in the left ventricle on the other hand (Wolter, Bayer & Quermann, 1955), provided that the mitral valves are not heavily calcified and therefore immobile (Moret, Schwartz, Arbeit, Grossman & Re, 1956). With due regard to the level of aortic pressure, a significant correlation has in fact been observed between the time interval second sound-opening snap and left atrial pressure (pulmonary-capillary-venous pressure) in measurements at rest (Wells, 1954; Wolter, 1954; Wolter, Bayer & Quermann, 1955; von Bayer, Loogen & Wolter, 1956). In these reports, the PCV pressure and phonocardiogram were recorded simultaneously to obtain maximum correlation, because of the risk that the level of the PCV pressure might undergo relevant changes within short time periods. It has also been observed that, in the upright position, the time interval second sound-opening snap is longer, indicating a lower left atrial pressure than in the horizontal position, whereas after short periods of muscular exercise it is shorter, indicating a higher left atrial pressure (Schölmerich & Gehl, 1951; Schölmerich & Schlitter, 1956). A corresponding relation between this time interval and PCV pressure was observed in cardiac arrhythmia (Schölmerich & Schlitter, 1954; Dittrich, 1956; Schölmerich & Schlitter, 1956). The effect of medical treatment or of mitral valvotomy in cases of mitral stenosis has even been evaluated as the change in this time interval (Schumann, 1954; Holldack & Heller, 1956; Steinzeig, Pinsky, Alimurung & Dimond, 1957).

It has been suggested (Wolter, Bayer & Quermann, 1955) that recording of the phonocardiogram during exercise might yield further information in cases of mitral stenosis but, apparently due to technical difficulties, recordings have hitherto been made only after the end of muscular exercise (von Bayer, Loogen & Wolter, 1956; Dittrich, 1956; Kunos & Garan, 1956). It is an old clinical principle to increase the cardiac output in cases of suspected mitral stenosis, in order to evoke or increase the pathognomonic diastolic murmur. This has usually been done by letting the patient perform muscular exercise before auscultation, and may possibly also be achieved by injection of sympathicomimetic drugs (Besterman, 1951). The old principle can be used to greater advantage by observing the patient during muscular exercise, e.g. during a work test on a bicycle ergometer of stepwise

a clinical diagnosis of isolated mitral stenosis.

BRA, brachial artery; m, mean; s, systolic; d, diastolic; es, endsystolic; OS, opening snap; 2S, aortic component of 2nd heart sound; TS, tight mitral stenosis; MS, moderately tight mitral stenosis; SR, sinus rhythm; FI, auricular fibrillation; FL, flutter.

mm Hg												
PCV, m/es	BRA, s/d	BRA–PCV, es	Pulm. resist., dyn.sec/cm^5	PHCG heart cycle, csec	Per cent diast.	Diast. LA–LV flow, l/min	2S–OS csec	LV relax. rate mm Hg/csec	Rhythm	2S–OS at cycle 80, csec	Mitral resist., mm Hg. min/l	Oper. obs.
30/46	96/64	26	1380	76–86	53–60	5.5–4.8	7.5	3.5	FI	7.4	5.9	TS
26/30	99/60	44	73	43	42	13.3	5.0	8.8	FL	9.4	2.0	TS
18/24	102/70	62	73	78	51	10.7	8.0	8.8	SR	8.2	1.7	TS
25/28	104/64	58	180	94	58	9.8	8.0	7.3	SR	6.4	2.6	TS
11/18	106/71	74	62	86	52	12.4	8.5	9.2	SR	7.8	0.89	—
18/28	117/77	66	—	47	43	21.2	5.0	13.2	SR	—	0.85	
21/29	106/60	53	320	84	55	7.8	9.0	5.9	SR	8.5	2.7	TS
19/22	109/64	57	43	70	51	14.6	5.5	10.3	SR	6.7	1.3	—
12/15	109/72	73	84	81	54	14.0	7.0	10.4	SR	6.9	0.86	—
23/27	119/79	71	108	54	48	21.5	4.5	15.5	SR	—	1.07	
11/16	110/66	73	42	87	53	10.7	10.0	7.3	SR	9.2	1.03	
26/30	136/81	76	25	51	43	14.6	5.0	15.2	SR	—	1.8	MS
9/10	112/72	90	57	88	52	16.1	9.0	10.5	SR	8.1	0.56	MS
23/29	131/79	76	—	53	45	38.0	4.5	16.8	SR	—	0.60	
22/26	113/71	64	610	90	57	7.6	8.0	8.0	SR	6.8	2.9	TS
—	131/78	—	—	59	51	8.8	6.0	—	SR	—	—	
24/28	113/78	67	170	81	55	8.6	6.5	10.3	SR	6.4	2.8	TS
32/43	128/72	57	370	63	55	11.3	5.6	10.5	SR	—	2.8	
28/34	114/66	53	720	52	40	14.3	7.0	7.6	SR	10.3	2.0	TS
27/33	120/84	82	341	61–85	44–60	9.0–6.7	7.5	11.0	FI	8.3	3.4	TS
35/42	123/90	73	695	37–58	46–52	10.4–9.2	—	—	FI	—	3.6	
15/19	121/67	81	84	100	58	13.1	8.0	10.1	SR	5.6	1.15	TS
26/29	150/80	83	90	73	51	19.3	5.0	16.6	SR	—	1.4	
33/35	180/83	95	51	57	51	21.2	2.5	38	SR	—	1.6	
17/22	129/65	76	222	70	50	11.6	8.5	9.5	SR	9.7	1.5	TS
26/30	146/69	78	139	46–75	39–65	11.8–7.1	6.0	13.3	FI	8.4	2.3	—
10/18	—	—	61	100	57	10.4	11.0	—	SR	8.6	0.96	—
8/14	—	—	148	60	43	12.5	8.0	—	SR	10.4	0.64	MS
22/28	—	—	180	92	59	5.3	7.0	—	SR	5.6	4.1	—
30/37	—	—	—	72	49	—	7.0	—	SR	8.0	—	—

(t_2 in Fig. 3) should denote the rate of relaxation of the left ventricle (Fig. 5). The time interval from the opening snap to the first heart sound, i.e., mechanical diastole, was expressed in per cent of the total heart cycle (Fig. 6) and the diastolic blood flow from left atrium to ventricle—assuming no mitral regurgitation to be present—was also calculated. In two patients (nos. 20/55 and 39/55, being nos. 35 and 33 in Holmgren, Jonsson, Linderholm, Sjöstrand & Ström, 1958) a small degree of mitral regurgitation was suspected from the clinical investigation, and the flow calculations may therefore be too low in these cases. The ratio a/b of (a) the average diastolic left atrial pressure gradient to the left ventricle (taken here as average PCV pressure above zero), and (b) the dia-

TABLE 1. Observations on 21 patients wi

Operation was performed on 14 of them; 11 were then found to have tight mitral stenosis, whereas th other 3 had moderately tight stenosis.

RA, right atrium; RV, right ventricle; PA, pulmonary artery; PCV, pulmonary capillary venous positio

Case no.	Sex	Age	BSA, m^2	Heart vol., ml	Total Hb, g	Blood vol., l	Work load, kgm/min	Pulse rate, beats/min	O_2 uptake, ml/min	A–V O_2 diff. ml/l	Cardiac output, l/min	Stroke vol., ml	Pressure RA, m	Pressure RV, s/d	Pressure PA, s/d
44/55	F	35	1.37	950	500	3.8	rest	100	220	75	2.9	29	12	103/12	103/67
36/54	M	36	1.80	860	650	4.4	rest	150	275	50	5.5	37	8	43/4	41/21
23/54	F	28	1.78	840	695	6.2	rest	110	180	33	5.5	50	−4	—	30/19
9/55	M	38	1.76	965	700	4.3	rest	68	283	50	5.7	83	4	60/4	59/26
43/55	F	29	1.76	930	590	4.8	rest	92	255	40	6.4	70	1	33/−1	26/11
							200	150	647	71	9.1	61	—	—	—
7/55	F	43	1.49	1010	510	3.6	rest	80	208	48	4.3	54	1	63/5	59/29
37/54	M	21	1.80	1200	910	5.8	rest	92	288	39	7.4	80	−1	35/0	35/19
39/55	F	39	1.67	735	685	4.8	rest	86	267	35	7.6	88	2	31/2	29/12
							200	118	740	71	10.4	88	5	55/7	52/25
41/55	F	40	1.62	790	450	4.0	rest	78	189	33	5.7	73	3	21/6	22/9
							200	136	477	75	6.3	46	—	41/4	39/22
18/56	M	35	1.82	1160	740	5.4	rest	73	310	37	8.4	115	1	23/1	22/10
							400	117	1418	82	17.3	148	0	46/0	46/19
21/55	F	38	1.68	1330	570	4.1	rest	79	220	52	4.3	54	−2	85/0	85/39
							100	136	428	96	4.5	33	—	135/13	135/68
9/56	M	42	1.78	1285	645	5.1	rest	130	274	57	4.8	37	3	39/2	43/29
							200	132	655	104	6.3	48	—	—	78/48
23/55	M	39	1.74	1080	630	4.2	rest	99	282	51	5.5	55	0	97/6	103/57
26/56	M	34	2.03	1600	1200	8.0	rest	98	289	73	4.0	41	2	62/2	62/4
							100	160	663	137	4.8	30	—	98/7	98/63
32/55	M	32	1.95	1040	980	6.4	rest	81	295	39	7.6	95	0	36/0	36/18
							200	108	729	75	9.8	100	−2	—	44/35
							400	133	1072	98	11.0	83	−4	—	45/38
17/55	F	42	1.62	1090	660	4.9	rest	79	249	43	5.8	73	0	54/−1	55/20
20/55	F	42	1.59	860	570	3.6	rest	98	213	46	4.6	47	1	53/3	52/26
10/54	M	34	1.76	1020	905	5.8	rest	65	243	41	5.9	91	0	—	23/10
7/54	F	38	1.54	570	550	4.0	rest	112	231	40	5.4	48	0	—	23/13
8/53	F	47	—	1070	615	5.2	rest	76	113	36	3.1	41	5	41/6	41/26
36/53	F	39	—	—	550	4.2	rest	111	212	—	—	—	—	—	55/32

terization and during the phonocardiographic study is shown.

Calculations

The average change in the 2S–OS interval with change in pulse rate (Fig. 3, lower part) was calculated, and using this figure the individual resting 2S–OS intervals were "corrected" to heart cycle 0.80 sec, i.e., heart rate 75 beats/min (Fig. 4, right). The endsystolic aortic pressure was next assessed as the endsystolic pressure in the brachial artery, and the gradient between "aortic" endsystolic pressure and "left atrial" endsystolic (taken as the PCV pressure maximum occurring slightly after the second heart sound) pressure (P_2 in Fig. 3) calculated. The ratio of this pressure gradient to the 2S–OS time interval

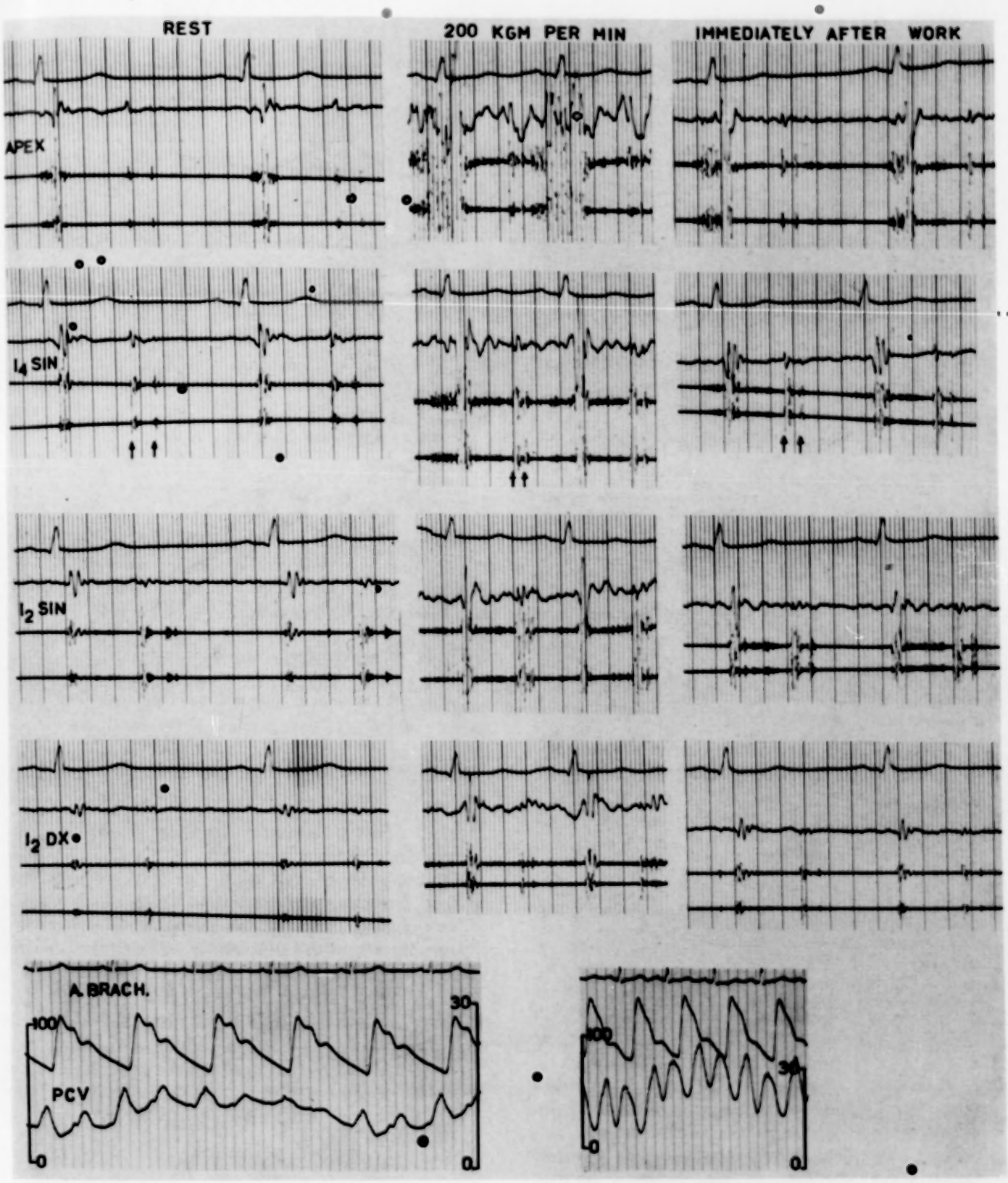


FIG. 1. A. A., a woman, 15-12-26, catheterization 41/1955. Mitral stenosis (Table 1). Phonocardiograms (each recording includes ECG lead I, and PHCG with differential amplification of low, medium and auditory frequencies) recorded over apex region, 4th L.I.S. at sternal border, 2nd L.I.S. at sternal border, and 2nd R.I.S. at sternal border. Recordings made with the patient supine, at rest, during and after muscular work (200 kgm/min) on a bicycle ergometer. Lower part of figure shows recordings in the supine position during right-heart catheterization: ECG, and blood pressure (mm Hg) in brachial artery and in PCV position in right lung. First recording at rest, second recording during muscular work.

Arrows mark beginning of aortic component of 2nd sound and of opening snap. Note increase in diastolic murmur and shortening of time interval between arrows during work.

stolic blood flow from the left atrium to the left ventricle, is an index of the resistance to flow of the mitral orifice. Such calculations (Gorlin & Gorlin, 1951; Gorlin, 1954) may be made in different ways (von Bayer, Loogen & Walter, 1953; Rodrigo, 1953), and the ventricular diastolic value may be assumed to be slightly higher than zero (Gorlin & Gorlin, 1951).

The aforementioned calculations are based partly on direct measurements, having experimental errors and biological variations, and partly on assumed values or conditions. Consequently, the calculations have an unknown but probably large error, and are used here mainly to point out possible ways of analyzing mitral stenosis. Direct recording of left ventricular pressures, made simultaneously with cardiac-output measurements and phonocardiographic recordings, are needed to demonstrate the possible accuracy and value of the calculations in question.

RESULTS AND COMMENTS

In all but one of the investigated cases of mitral stenosis, the apical diastolic and presystolic murmur increased during work (in a few cases it appeared). The appearance or accentuation of a diastolic murmur was of qualitative diagnostic value in a few of the patients with mild or moderate stenosis. The opening snap always moved closer to the second sound during work (Figs. 1 and 2, Table 1). The relation obtained between the time interval 2S–OS and the values of PCV mean pressure, observed during catheterization, is shown in Fig. 4.

The values at rest show considerable scatter. This might be ascribed to the fact that the phonocardiograms were recorded during catheterization only in a minority of cases, and that the pulse was then usually higher (by an average 13 beats/min at rest and 22 beats/min during work) than during phonocardiographic recording. The scatter was, however, increased by relating the time interval to a common heart rate (Fig. 4, right; Wells, 1954). The highest PCV pressure was noted in a patient (no. 44/55) who had very low stroke volume and high pulmonary vascular resistance, as well as auricular fibrillation. Her 2S–OS interval at rest (average ventricular rate 74) was 7½ csec. At catheterization the average ventricular rate was 100; the 2S–OS interval "corrected" to this heart rate would be about 4½ csec, which is a value better corresponding to the high PCV pressure. The scatter in Fig. 4 (left) may thus be somewhat decreased by relating the 2S–OS time interval to the actual heart rate at catheterization.

The arterial blood pressure at rest differed in the respective patients, but no consistent relation was observed between the level of systolic or diastolic arterial pressure and the time interval between second sound and opening snap. (See Table 1, where the cases are arranged in rising order of arterial systolic pressure at rest.)

During work, the PCV pressure rose regularly in these cases, and the time interval second sound-opening snap always became shorter (Figs. 1–4). In Fig. 3 the relation obtained between pulse frequency and time interval is shown. With rising work loads and

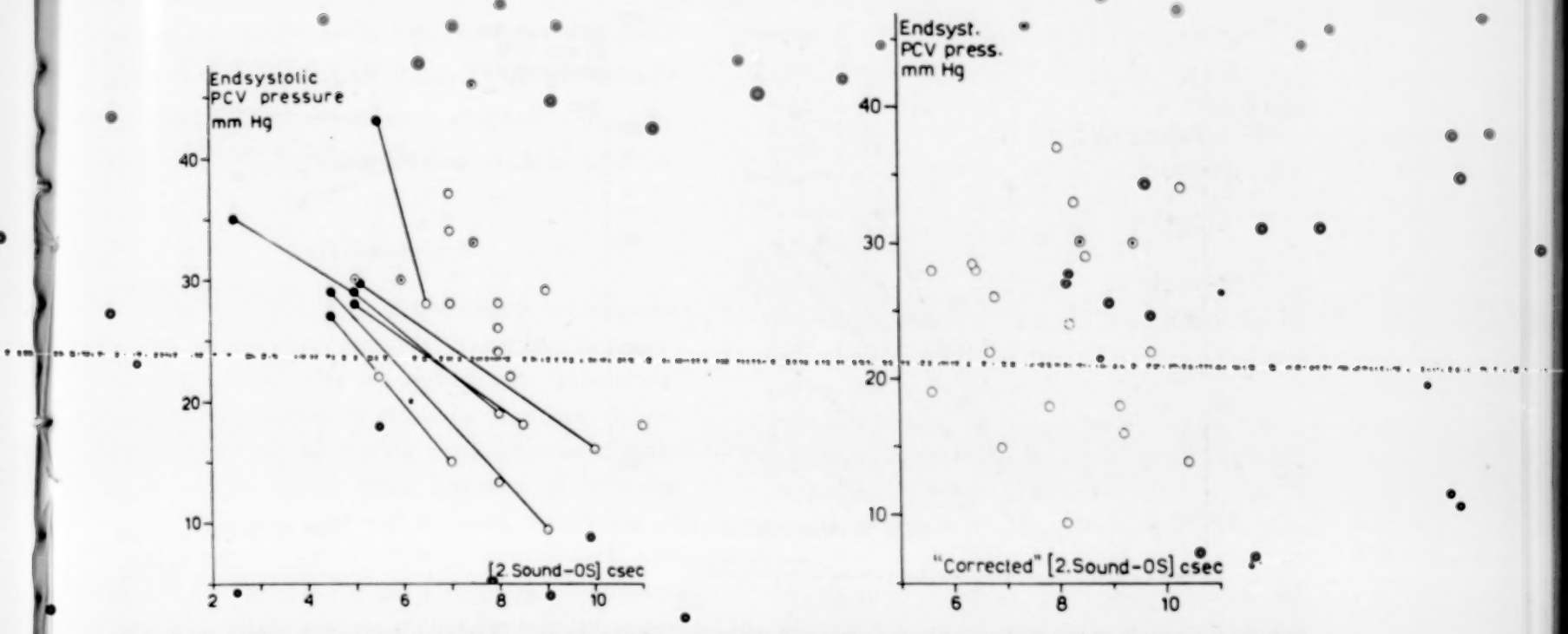


FIG. 4. Relation between time interval (csec) from beginning of aortic component of 2nd heart sound to beginning of opening snap (abscissa) and endsystolic pressure (mm Hg) in PCV position during right-heart catheterization (ordinate): values in 21 cases of mitral stenosis. Observations with patients in supine position, at rest (open circles) and during muscular work on bicycle ergometer (filled circles). A straight line joins values recorded in the same patient at rest and during work. Four patients with auricular fibrillation or flutter (dotted circles) are included. The other patients had sinus rhythm. The left-hand part of the figure shows values actually recorded, irrespective of heart rate. In the right-hand part, the sound intervals (abscissa) have been recalculated to a heart rate of 75 beats/min.

toms, and there was also a more frequent occurrence of high PCV pressure in such cases. The opening snap was less easily audible in cases with high pulmonary resistance, which is a common experience, although the PCV pressure was relatively high. This has been suggested to be at least partly due to the frequent occurrence of significant calcification of the mitral cusps at this stage of the disease, leading to decreased valvular mobility.

In one of the five patients examined by right-heart catheterization and by phonocardiography during work, the diastolic murmur decreased during muscular work, and the opening snap disappeared or became indistinguishable from the second sound. This patient had high PCV pressure and pulmonary vascular resistance, and during the work test an incipient attack of pulmonary edema occurred. For this reason, a work test was not made in the catheterization study; consequently, we do not know whether a diminution of cardiac output occurring during work was responsible for the unusual phonocardiographic change.

The apparent "rate of relaxation" of the left ventricle was found to increase during work with rising pulse rate (Fig. 5, left), but also appeared to be dependent on the aortic-atrial pressure gradient (Fig. 5, right) both at rest and during muscular work.

As described under Methods, the cardiac output was recalculated to rate of blood flow during diastole. During muscular work the pulse rate rose, cardiac output usually increased moderately, and the percentage duration of

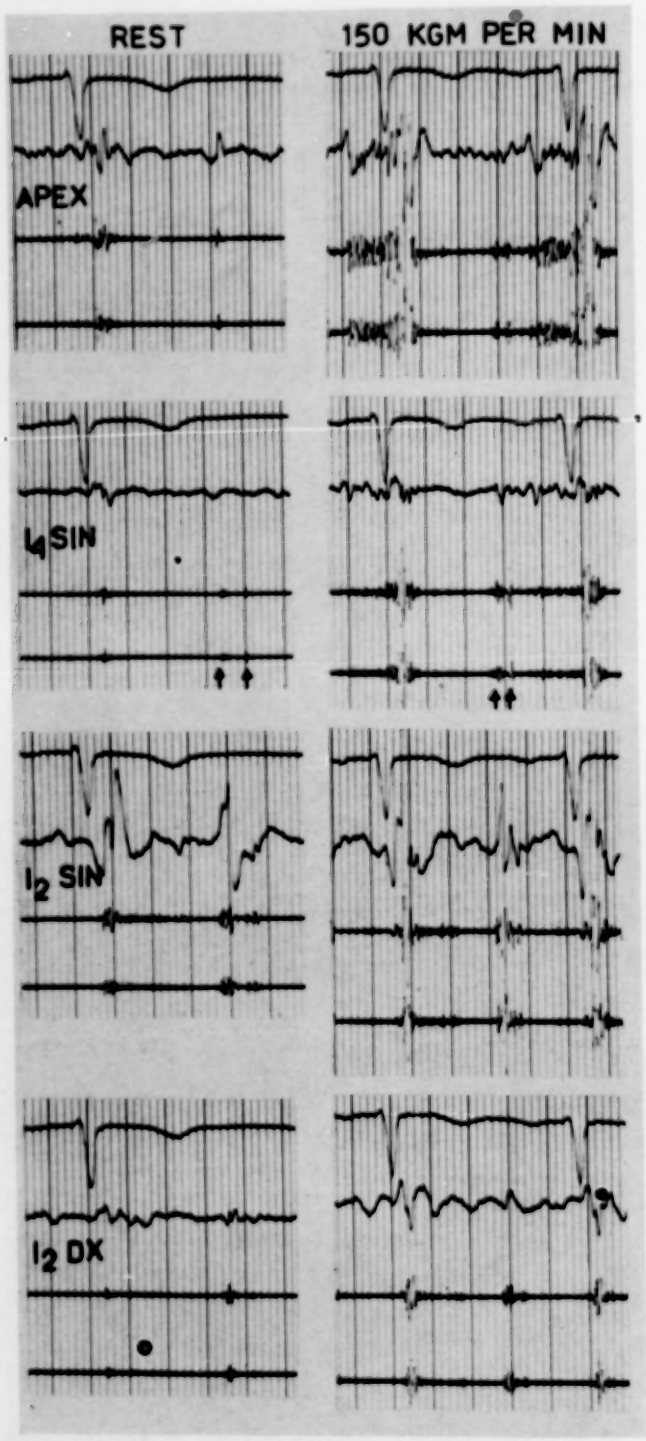
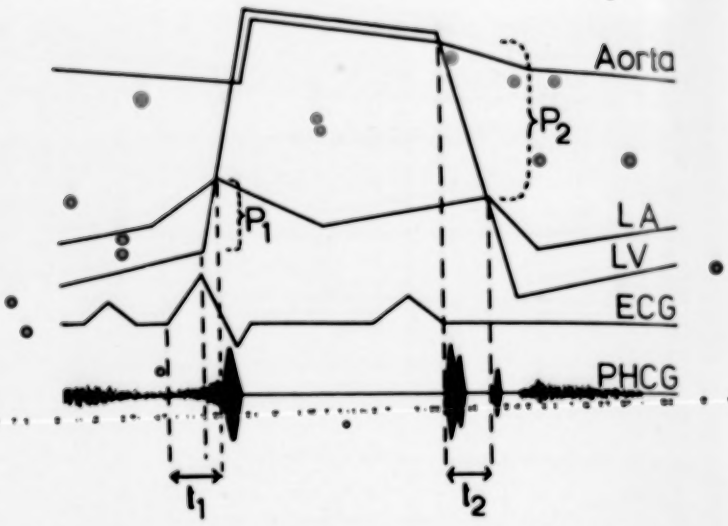


FIG. 2. H. A., a woman, 32–09–16. Mitral stenosis + pregnancy (4th month). Phonocardiograms recorded in supine position, at rest and during work on bicycle ergometer. Further explanation: see Fig. 1. Note increase in diastolic murmur and shortening of time interval between arrows during work.



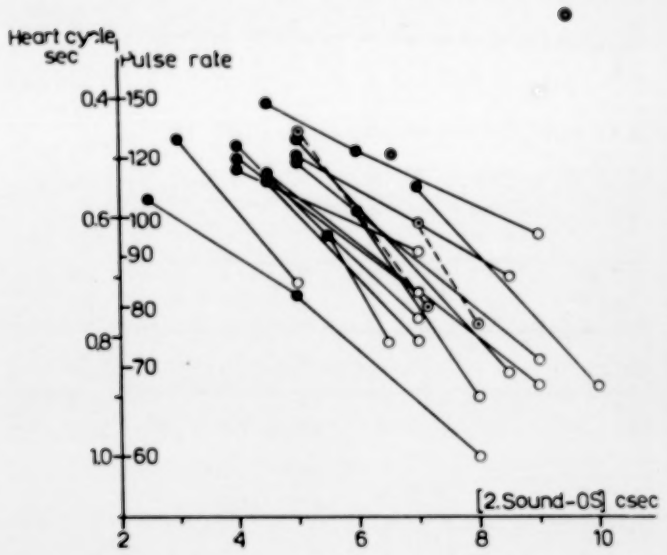


FIG. 3. *Top*: Schematic drawing illustrating dependence of the two time intervals, i.e., from R wave on the ECG to 1st heart sound (t_1), and from aortic component of 2nd heart sound to opening snap (t_2), on the difference between enddiastolic left-ventricular and atrial pressures P_1) and endsystolic aortic and atrial pressures (P_2), respectively. *Bottom*: Relation between time interval from aortic component of 2nd heart sound to opening snap (abscissa) and heart rate or duration of heart cycle (ordinate): values in 16 cases of mitral stenosis; recordings made at rest and during muscular work. Symbols as in Fig. 4.

shorter 2S–OS time intervals, it became increasingly difficult to distinguish the snap in the phonocardiogram as it entered into the later oscillations of the second sound. It was even more difficult to differentiate the two sounds from one another by auscultation (Holldack & Wolf, 1956).

No apparent correlation existed between pulmonary vascular resistance and 2S–OS time interval at any given level of PCV pressure. Cases with increased pulmonary resistance usually represented longer duration of symp-

pressure rose with increasing diastolic flow with an inclination (Fig. 6) which is probably directly related to the obstruction to flow in the mitral orifice.

SUMMARY

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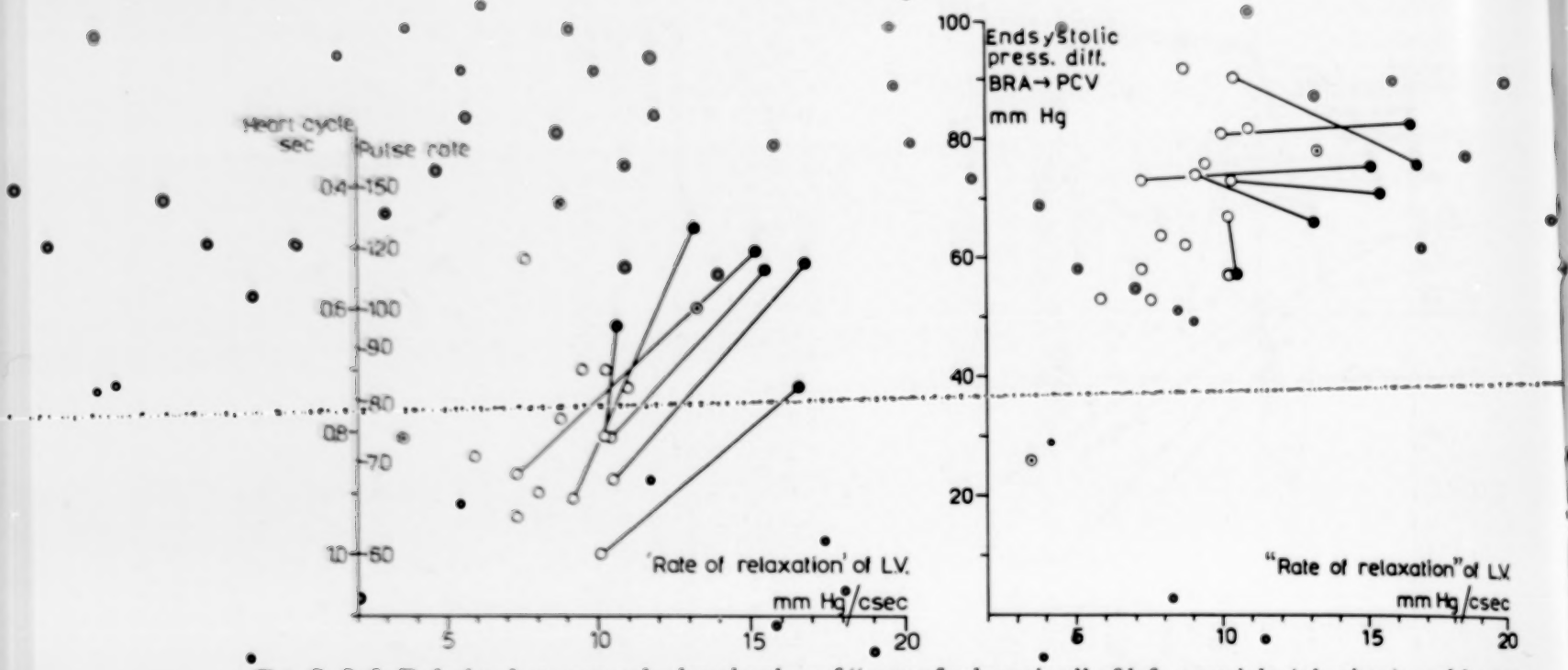


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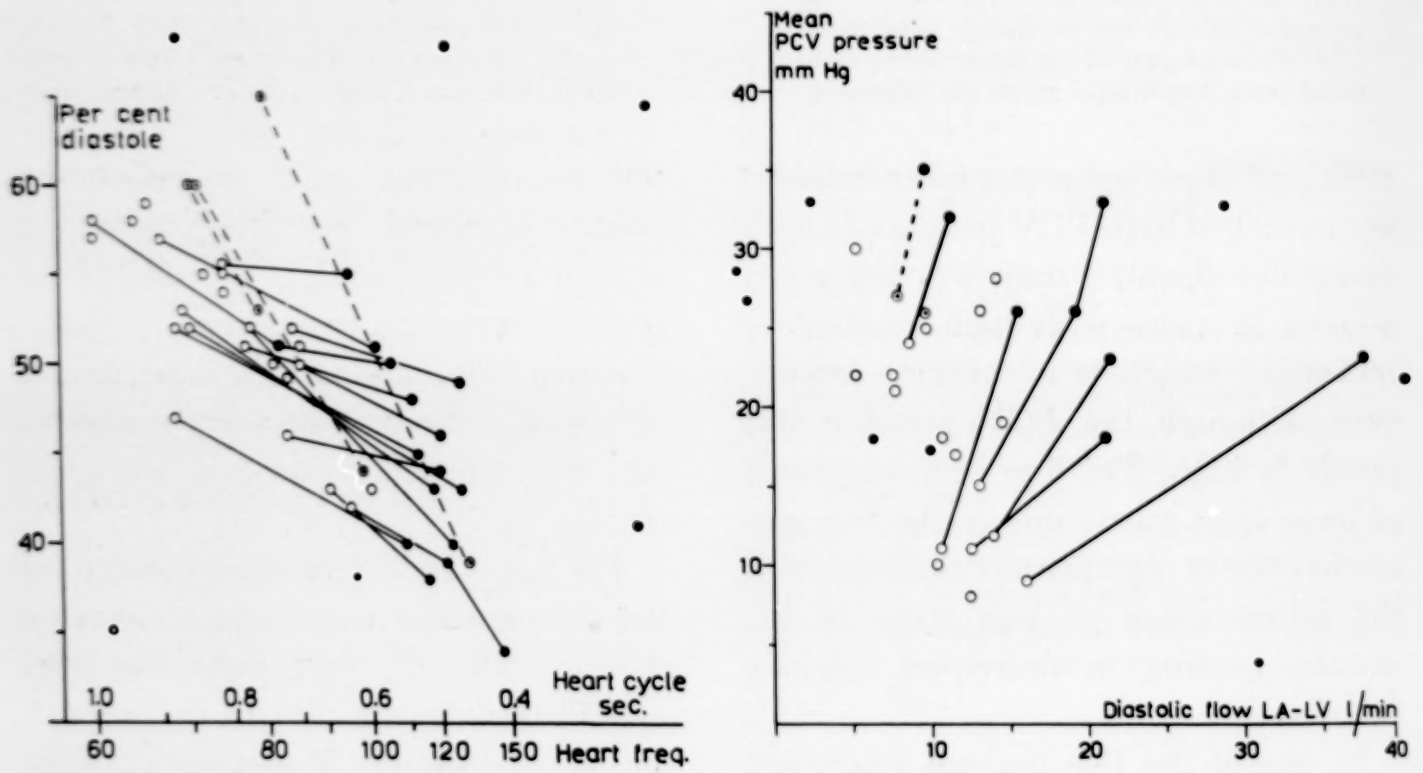


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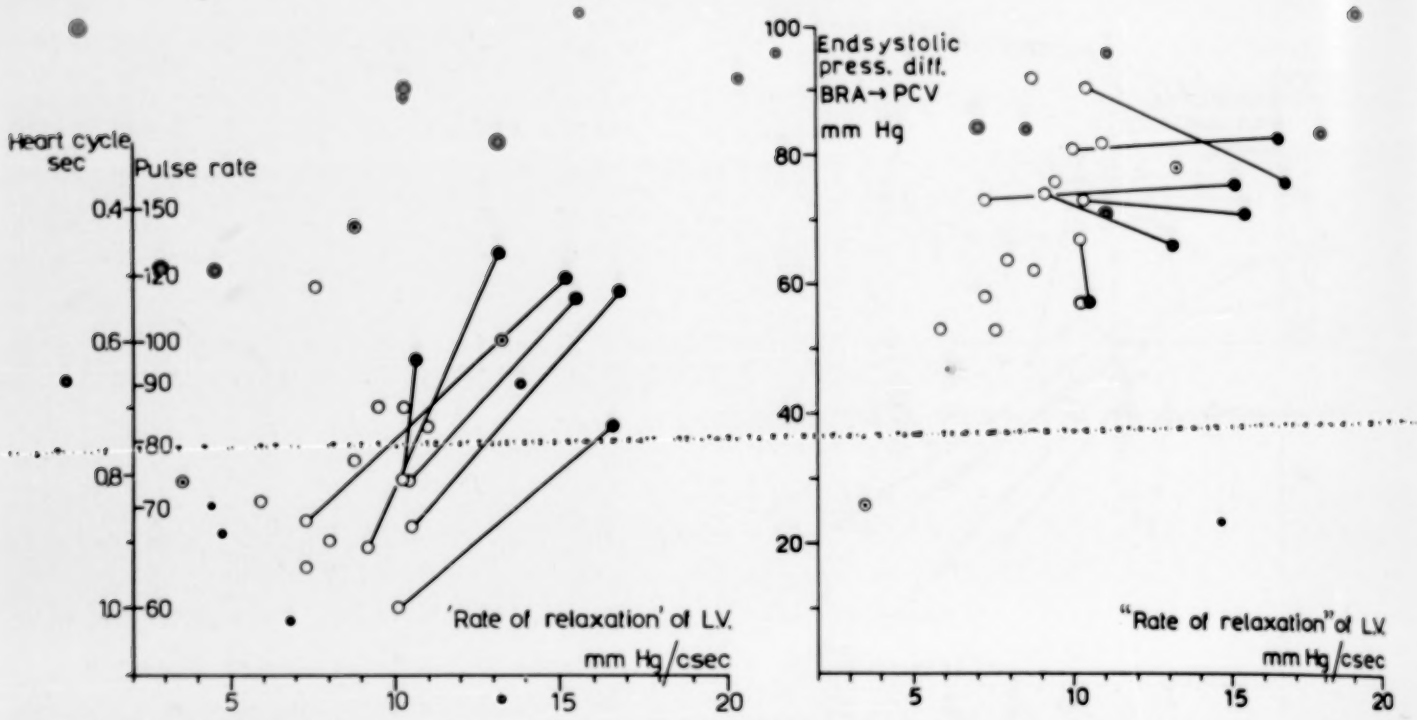


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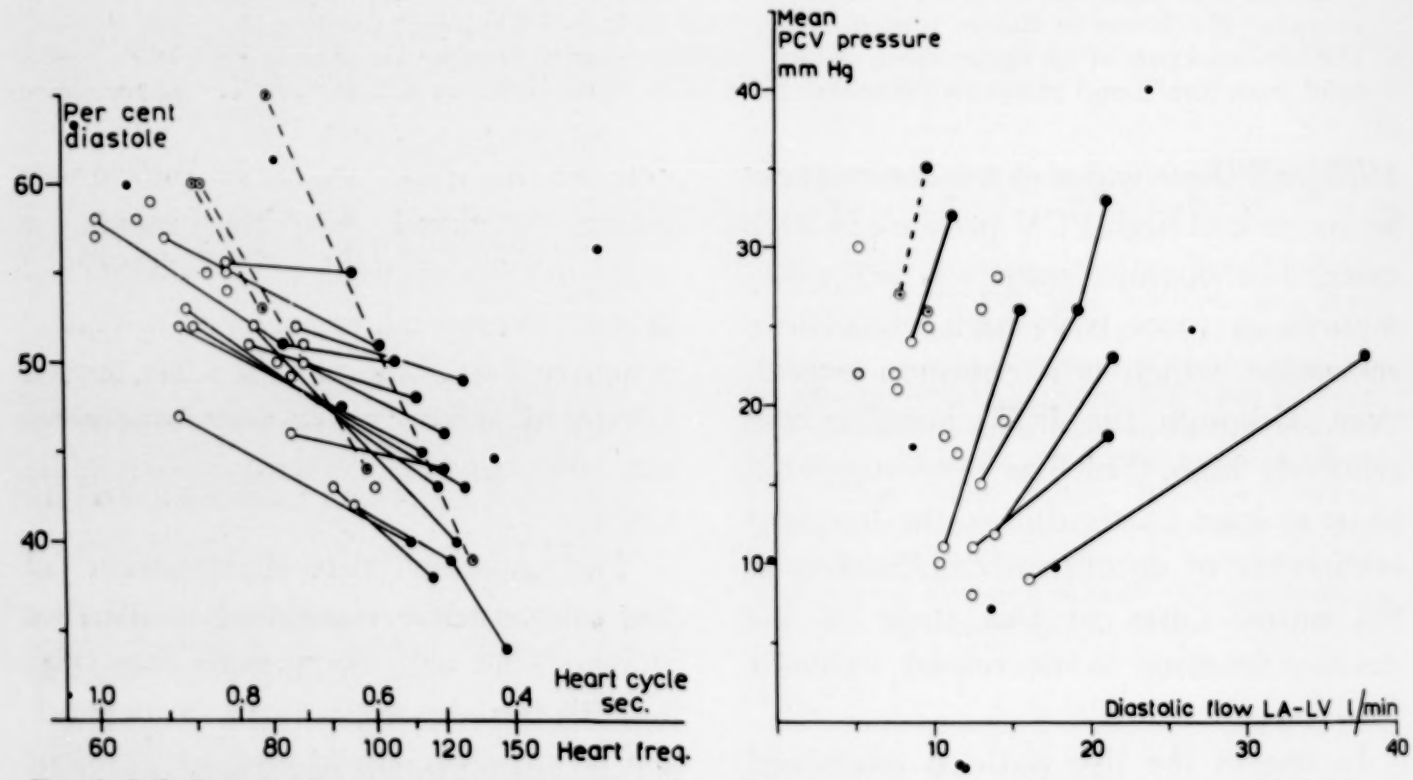


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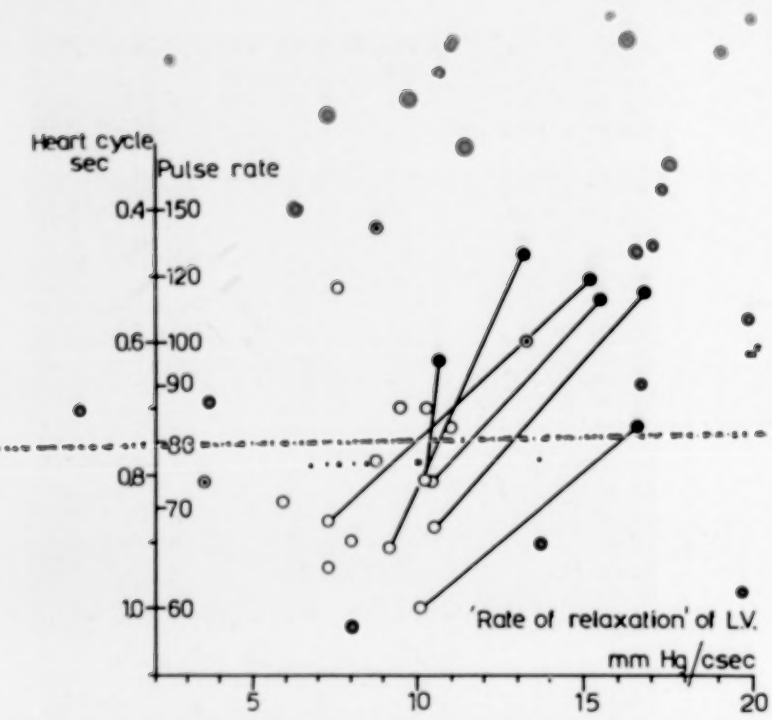
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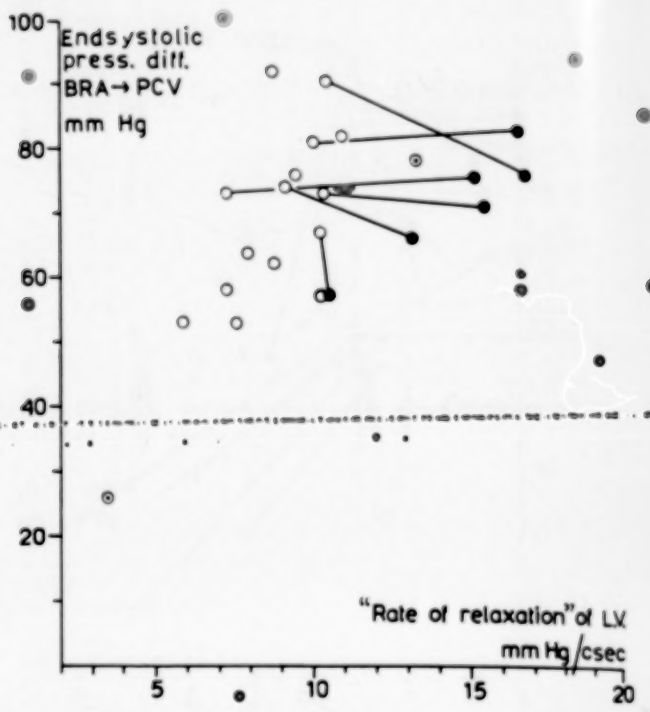
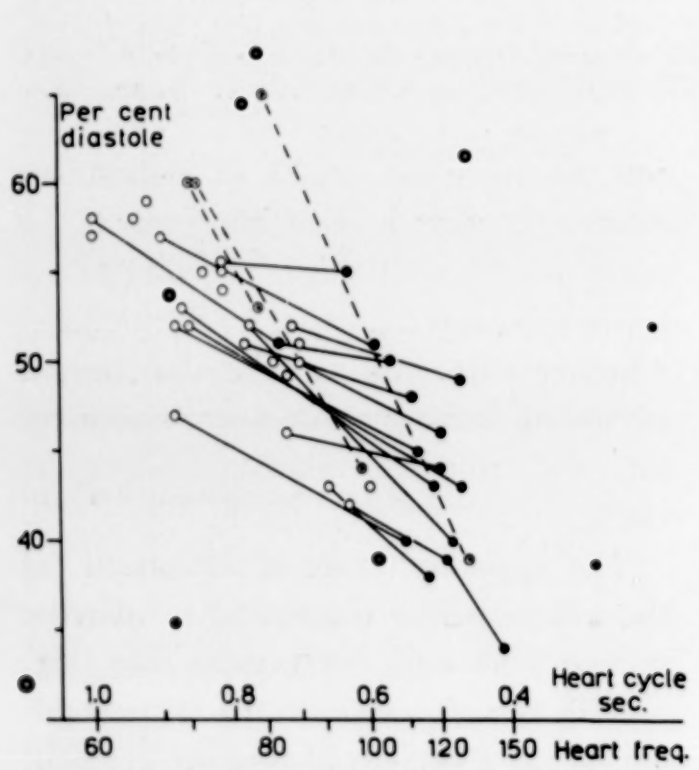


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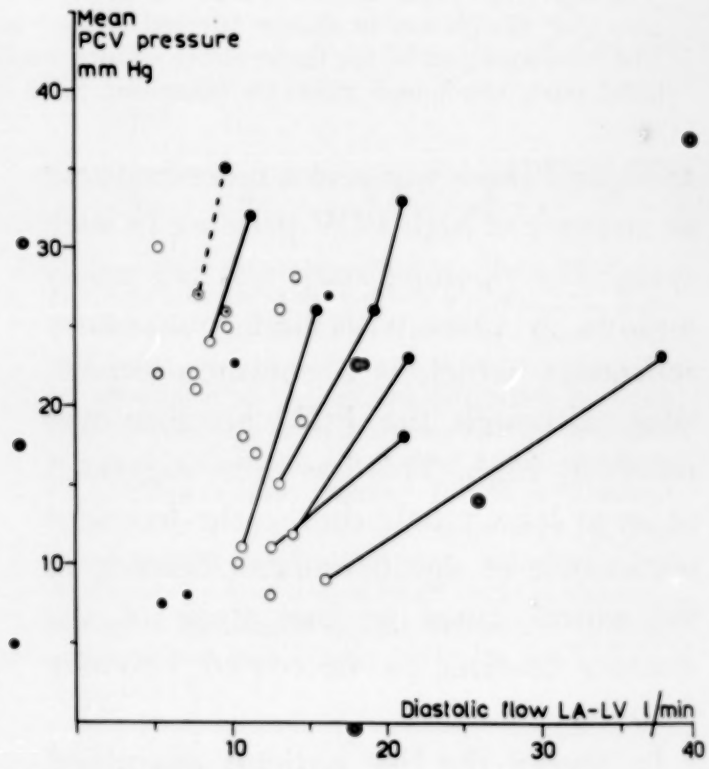


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From the University Clinic, Surgical Department R, Rigshospitalet, and the Queen Louise Children's Hospital, Copenhagen, Denmark

Ventricular Septal Defects in Infants Treated with Various Modifications of the Dammann–Muller Operation

F. THERKELSEN, P. A. GAMMELGAARD and I. BOESEN

The prognosis for children with ventricular septal defects depends on the size of the defect and presumably also on the condition of the pulmonary vessels.

Experience shows that the prognosis is good when the defect is small and the heart of normal size or only slightly enlarged. Most of these patients may lead a normal life and have apparently the same life expectancy as other individuals (I. D. Keith *et al.*, and others).

On the other hand, the prognosis is less hopeful for infants with large defects, increased pulmonary flow and pulmonary hypertension. Many of these patients die at an early age; according to I. D. Keith *et al.*, most of them succumb within the first year of life. A. S. Nadas emphasises that the prognosis is poor in the presence of a markedly increased blood flow and increased pressure in the pulmonary artery, and C. Crafoord claims that the outlook depends to a very great extent on the size of the defect. That many of these children die at an early age appears from the report by I. Boesen & S. Vendel on a series of 1145 autopsied children who died from congenital heart disease before the age of 4 years.

Of these children, 1084 (95 %) died before the age of 12 months; ventricular septal defects (sometimes associated with atrial septal defect (secondary defect) and/or patent ductus arteriosus) were present in 21 % of these 1084.

Nearly all these patients presented large ventricular septal defects with considerable cardiac enlargement; more than one half of them died before the age of 5 months.

Thus, there is a group of infants with ventricular septal defects in whom treatment must be instituted within the first 6 months of life, if they are to be given any treatment at all. The group of infants in whom the prognosis is particularly grave comprises the cases with a large defect and a large shunt associated with increased pressure in the right ventricle, possibly equal to that in the left ventricle. In some of these infants, the pulmonary resistance may gradually become so great that the direction of the shunt is reversed, by which their disease changes into an Eisenmenger complex,

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autopsied cases reported by I. Boesen & S. Vendel show that if these patients die, death occurs at a very early age.

2. In infants with a ventricular septal defect, considerable pulmonary hypertension and pronounced cardiac insufficiency, conservative treatment has, at best, only a transient beneficial effect. Many of the infants had to be operated on, because it was a question of life and death evidenced by rapid deterioration of the condition during a brief period of observation.

3. The infants with ventricular septal defect and pulmonary hypertension who improved during conservative treatment for a short period were not subjected to operation, but served as a control series.

Among the 238 children under 2 years of age who were subjected to heart catherisation and angiocardiography, 78 revealed isolated ventricular septal defect (sometimes associated with a secondary atrial septal defect). Operation was performed in 22 of these, who all had pulmonary hypertension and were in a very poor condition. Among the remaining 56, 12 were in a good general condition, but had a systolic pressure in the pulmonary artery exceeding 40 mm Hg. Of the remaining 44, who all had pulmonary hypertension (31 even a systolic pressure exceeding 60 mm Hg), it is known that at least 15 succumbed. A more detailed report will be published later.

4. The Dammann–Muller operation seems to be well-founded as a palliative measure. We considered the operation indicated in children with ventricular septal defect, enlarged heart, pulmonary congestion and a large left-to-right shunt

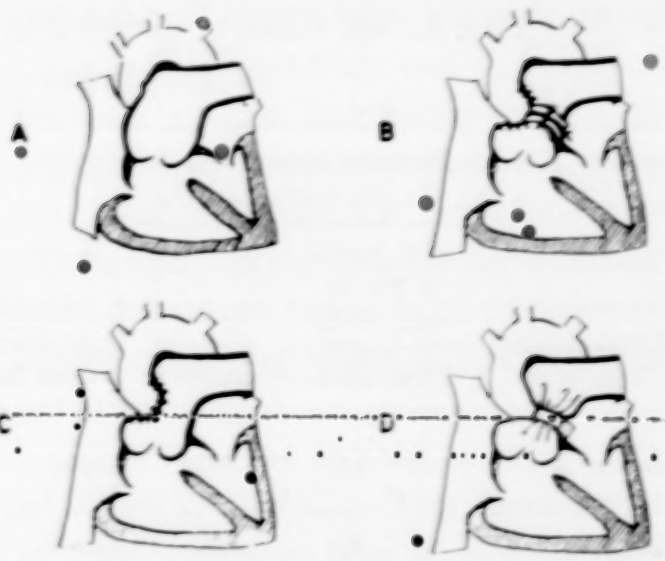


FIG. 1. (A) Ventricular septal defect with pulmonary hypertension. (B) The original Dammann–Muller method. (C) Modified Damman–Muller method—only a segment excised of pulmontary artery. (D) Albert's modification of the Dammann–Muller method—only band around pulmonary artery.

demonstrated by heart catheterisation —usually with pressure equalisation between the ventricles—when conservative treatment had failed to give any improvement or, rather, had resulted in an aggravation of the condition.

The original Dammann-Muller operation consists in segmental excision of the pulmonary artery supplemented by application of a polyethylene band around the narrowed portion (Fig. 1B). The surgical narrowing of the pulmonary artery is performed to such an extent that pressure measurements during the operation show a reasonable gradient between the pressures proximal and distal to the narrowed portion—and so that the pressure peripherally approaches normal pulmonary pressure.

However, the operation involves the risk that the stenosis gradually becomes relatively too narrow, so that the heart disease changes into a Fallot-like type

so that the patients must be considered to be beyond the reach of surgical therapy.

In very poor infants with ventricular septal defect and a left to right shunt, the rational treatment would obviously consist in surgical closure of the defect in open cardiotomy, but experience shows that such a radical operation is very hazardous (I. W. du Shane; I. W. Kirklin *et al.*; D. C. Fyler). However, D. A. Cooley *et al.* reported a mortality of only 7 deaths in 20 operations for ventricular septal defects in infants under 12 months of age.

From a study published by H. A. Zimmermann *et al.* it appears that death occurred in all of the relatively few infants with pressure equalisation within this age group whom they subjected to operation.

We have also performed radical operation in infants with ventricular septal defect, a large shunt and pressure equalisation between the ventricles, using the Rygg–Kyvsgaard heart-lung machine, but all these critically ill infants succumbed.

The question then is if some sort of palliative treatment may carry the children through the first years of life, so that they can stand radical operation, which must be considered to be less dangerous at a somewhat more advanced age.

Some investigators (D. C. Fyler *et al.*; A. S. Nadas) claim that it is possible to obtain such good results by medical treatment that palliative operation during infancy is indicated only in extreme cases.

In some cases of the present series, digitalisation was given a trial in infants with pronounced cardiac insufficiency, combined with antibiotic therapy for pulmonary complications, but, at best, merely a transient effect was observed.

In 1954, we (F. Therkelsen *et al.*) changed over to the Dammann–Muller operation, in which surgical narrowing of the pulmonary artery is performed as a palliative measure. The object of this operation is twofold, viz. to protect the lungs against the large pulmonary flow and the resultant overload of the heart due to the ventricular septal defect, and to a greater extent to divert the blood stream through the systemic circulation.

By this operation it may presumably be possible to avoid the development of changes in the pulmonary vessels, which were present in a severe degree in many of our patients (V. Eskelund & Therkelsen), or to lessen such changes as have already developed, resulting in an improvement of the prognosis. F. Dammann & W. H. Muller expressed the view that this would be possible. However, the investigations reported by A. S. Nadas, D. C. Fyler *et al.* and others suggest that the pulmonary resistance during growth can be changed only to a very slight extent in children with ventricular septal defect in whom the changes in the pulmonary vessels may be assumed to occur owing to the large pulmonary flow.

The justification of using a palliative operation in infants may be summarized as follows:—

1. In our opinion, the prognosis of severe ventricular septal defect is very grave without operative treatment, and, as previously pointed out, the studies on

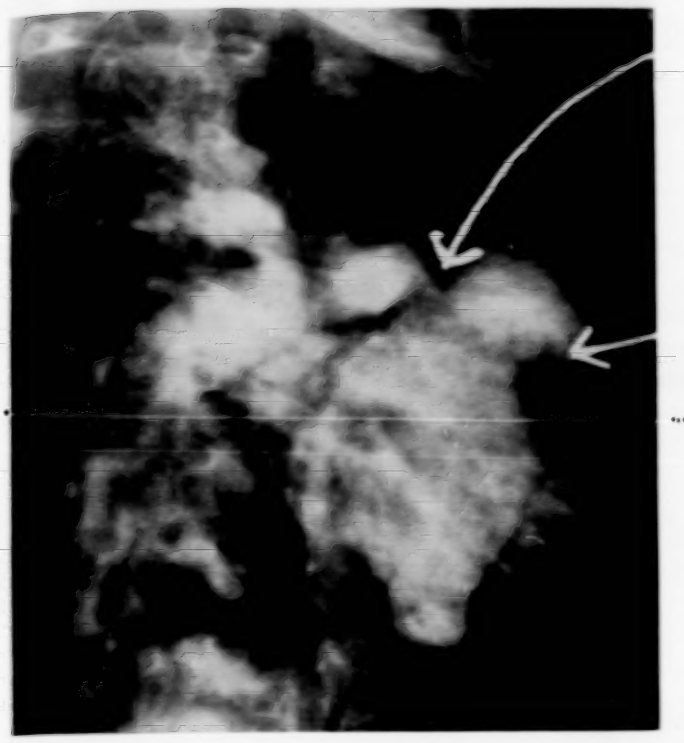
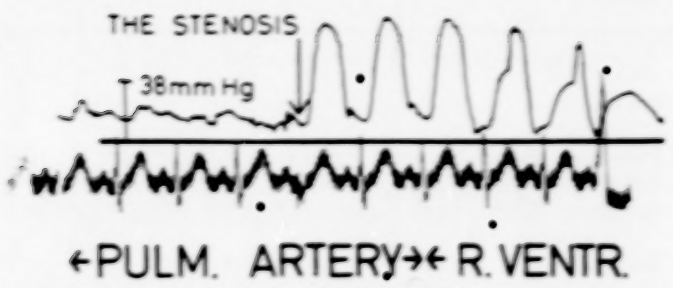


FIG. 2. *Ventricular septal defect.* B. L. N., 5 months old. Dept. R, 20.7.55: Op. Dammann–Muller. (*a*) *Angiocardiography*, 2 years postop. Upper arrow: artif. sten.; lower arrow: pulm. valv.



(*b*) Same patient, *pressure curve* at the cardiac catheterisation, 2 years postop.

slight narrowing, which gave a gradient of only 10 mm Hg. The cause of the postoperative death in this patient may be that the changes in the pulmonary vessels were so pronounced that the patient did not tolerate a reduction in the pressure to 77 mm Hg. However, histological examination of a pulmonary biopsy specimen showed only questionable changes. The ventricular septal defect measured only 5 × 5 mm.

II. *Six infants subjected to the modified Dammann–Muller operation* (Table 2).—In this operation, only a segment of the pulmonary artery was excised. In all cases, a good gradient and a peripheral pressure in the pulmonary artery approaching normal were obtained. However, the mortality was high; in 1 case, death was due to sudden haemorrhage from the suture canals in the pulmonary artery occurring when a Derras clamp was removed.

III. *Ten infants operated on by the method of Albert* (Table 3).—This modification is a less extensive type of surgical intervention, since resection of the pulmonary artery is not performed, and it is claimed to facilitate a later radical operation. It appears that the infants much better stand this type of operation, because the cardiac action is affected to a lesser degree, and the mortality seems to be appreciably lower. A suitable fall in the pressure is easily obtained peripherally in the pulmonary artery.

However, a fall in pressure amounting to only 5 mm Hg was tolerated in 1 case.

Follow-up studies (Tables 1–3)

Surgical narrowing of the pulmonary artery was performed in a total of 22 cases; 10 deaths occurred, including 7 in the first two groups. Of the 12 survivors, 9 were followed up after observation periods ranging from 6 months to 4 years (in 3 cases, the observation periods were relatively short).

In 4 cases, the condition was excellent; the children thrived well (showing normal weight curves); only slight dyspnoea developed on exertion and cyanosis was absent. The size of the heart had returned to near-normal.

In 3 cases, the condition was good; physical development and the size of the

TABLE 1. Six cases of ventricular septal defect subjected to the original Dammann–Muller operation.

Case, age at operation	Pressure measurements on the table, mm Hg: Syst. press. in rel. to narrowing, Prox.	Dist.	Gradient	Condition at discharge from hospital	Follow-up examination: Length of obs. period, years	Cardiothoracic index: Pre-op.	f.-up	Clinical condition
Birthe R., 6 mos.	97	67	30	Good	4	64	56	Good
Pia W., 7 mos.	84	40	44	Good	4	69	57	Excellent for 3 yrs., then deteriorating with cyanosis
Linda P., 12 mos.	77	33	44	Died, autopsy VSD 8 × 10 mm		67		
John A., 8 mos.	80	19	61	Died, autopsy VSD 10 × 10 mm		70		
Lilli P., 23 mos.	87	77	10	Died, autopsy VSD 5 × 5 mm		70		
Bernh. L. N.,	76	25	51	Good	3½	68	54	Excellent

with cyanosis, if the pressure in the right ventricle exceeds that in the left ventricle.

After the lapse of some time, we therefore modified the technique, so that we only excised a segment of the pulmonary artery, whereas we did not apply a band around the narrowed portion (Fig. 1 C). However, as this method, like the original form of the operation, resulted in a relatively high mortality and rendered later radical operation difficult, a further modification of the method was adopted (H. M. Albert). Accordingly, in the last operations performed, we only applied a band around the pulmonary artery and tightened it until a suitable pressure gradient was obtained (Fig. 1 D). It is claimed that this modification gives the advantages that the mortality is reduced, and that it is relatively easy to unfold the pulmonary artery when the band is removed at a subsequent radical operation, which is reported to have been shown experimentally (H. M. Albert).

In order to illustrate the effect of the various forms of surgical narrowing of the pulmonary artery we report below our follow-up studies on patients with postoperative observation periods ranging from 6 months to 4 years.

OPERATIONS AND FOLLOW-UP STUDIES

1. *Six infants subjected to the original Dammann–Muller operation* (Table 1).— In 5 cases, a good gradient and a satisfactory fall in pressure in the pulmonary artery peripheral to the stenosis were obtained (Fig. 2 *a* and *b*). In 1 case (Lilli P.), the infant tolerated only a

TABLE 3. Ten cases of ventricular septal defect subjected to Albert's modification of the Dammann–Muller operation.

Case, age at operation	Pressure measurements on the table, mm Hg: Syst. press. in rel. to narrowing, Prox.	Dist.	Gradient	Condition at discharge from hospital	Follow-up examination: Length of obs. period, years	Cardiothoracic index: Pre-op.	f.-up	Clinical condition
Henrik H., 8 mos.	76	36	40	Good	1½	69	60	Good
Toni H., 7 mos.	60	55	5	Good	½	62	63	Fair
Ove M., 7½ mos.	86	50	36	Good	¾	60	51	Excellent
Eivind G. H., 5½ mos.				Died, autopsy VSD 3 × 5 mm				
Ellen J., 3 mos.	70	40	30	Good	¾	64	57	Excellent
John K. J., 5 mos.	100	75	25	Good		64		Died shortly after discharge (pneumonia)
Lola P., 3½ mos.	73	56	17	Recently operated on. Satisf.		67		
Kim H., 10 mos.	79	53	26	Died; no autopsy		63		
Kim A., 3 mos.	82	44	38	Recently operated on. Satisf.		65		
Svend J., 7 mos.	62	38	24	Recently operated on. Satisf.		61		

DISCUSSION

In 22 cases of ventricular septal defect, in which disease the prognosis without operation, in our opinion, is very grave, surgical narrowing of the pulmonary artery seems to have opened a possibility to carry some of these patients through infancy, in which radical operation is fraught with dangers. The improvement persists for a prolonged period, provided that a sufficient reduction in the pulmonary pressure is obtained. The only case in which the pressure was reduced by only 5 mm Hg did not show any improvement. In Bia W., considerable improvement during the first 3 years was followed by gradual development of cyanosis, but this was only to be expected in view of the absence of growth of the narrowed portion of the artery (Fig. 3). It must be admitted that it had not been possible to catheterise the pulmonary artery peripheral to the stenosis; accord-

TABLE 2. Six cases of ventricular septal defect subjected to the modified Dammann-Muller operation (only excision of a segment of the pulmonary artery).

Case, age at operation	Pressure measurements on the table, mm Hg: Syst. press. in rel. to narrowing Prox.	Dist.	Gradient	Condition at discharge from hospital	Follow-up examination: Lenght of obs. period, years	Cardiothoracic index: Pre-op.	f.-up	Clinical condition
Bente N., 6 mos.	68	35	33	Good	3½	61	55	Good
Lone A., 4½ mos.	98	30	68	Good	3½	60	56	Excellent
Bjarne T., 3 mos.	45	26	19	Died, autopsy VSD 7 × 12 mm				
Kaj M., 4 mos.	80	39	41	Died, autopsy VSD 3 × 6 mm		67		
Børge B., 2 mos.	63	24	39	Died, autopsy VSD 4 × 8 mm		65		
Frank J., 8 mos.	106	68	38	Died, autopsy VSD 8 × 12 mm				

heart had approached normal, and the general condition was good. However, the children showed slight dyspnoea at rest, but cyanosis was absent.

In these 7 children a good gradient in the pulmonary artery had been obtained at operation.

In 1 case, the condition could merely be described as satisfactory. The child thrived fairly well, but rather pronounced dyspnoea was present. The heart had not decreased in size. The explanation of the absence of improvement in this case presumably was that the patient at operation had tolerated only a relatively slight narrowing (gradient 5 mm Hg). It is true that in this case the observation period was only 6 months, but in all the other cases the improvement, if any, had occurred within the first few months after operation.

In none of the 8 cases considered above was cyanosis observed at the follow-up examination. On the other hand, in the last of the 9 cases subjected to follow-up examination it appeared that the child had shown considerable improvement during the first 3 years, so that, according to the statements of the parents and the results of a follow-up examination at that time, it was practically normal as far as physical development, heart size and general health were concerned, but during the fourth year after operation the condition showed slow deterioration, with increasing dyspnoea and, especially, cyanosis. (Pia W., Fig. 3.)

Bente N. (Fig. 4*b*) 3½ years postoperatively and in Bernh. L. N. (Fig. 2*b*) 2 years postoperatively we found unchanged pressure in the pulmonary artery peripheral to the stenosis. At the follow-up examination, the condition in these two children was "good" and "excellent," respectively, and cyanosis was absent. In Bente N., who underwent operation by the modified Dammann–Muller method, there might be a certain risk of subsequent dilatation of the surgically narrowed portion of the pulmonary artery. However, the results of heart catheterisation and angiocardiography at the follow-up examination seem to show that this had not occurred (Fig. 4*a* and *b*).

Radical operation, which may later be considered in all these patients, has in some of the cases been rendered difficult because the original Dammann-Muller operation and its first modification may require some form of plastic surgery on the pulmonary artery, whereas the modification devised by Albert must be assumed to give better possibilities of radical operation.

SUMMARY

Some studies on the use of the original Dammann–Muller operation and two modifications are reported. These operations were employed as a palliative measure in infants with ventricular septal defects and markedly increased pressure in the pulmonary artery after conservative treatment had failed to bring about any improvement. A total of 22 infants were subjected to operation, with 10 primary deaths. However, among the last 10 patients who underwent operation, only 3 deaths occurred. Nine patients were followed up after observation periods ranging from 6 months to 4 years: seven showed excellent or good results, whereas the results could merely be described as satisfactory in 1 case. In 1 case, considerable improvement during the first 3 years was followed by a downward course with increasing cyanosis. It is emphasised that after the lapse of some years, the palliative operation must presumably be followed by radical operation in open cardiotomy.

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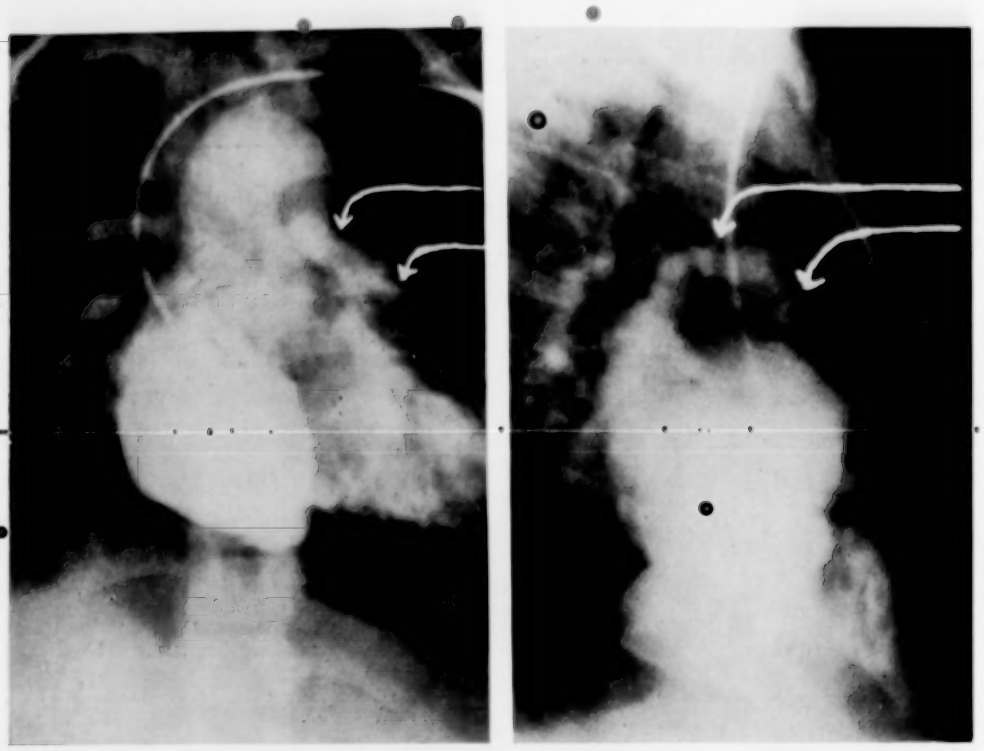


FIG. 3. *Ventricular septal defect.* Pia W., 7½ months old. Dept. R, 7.12.54. Op. Dammann–Muller. *Angiocardiography*, 4 years postop. Upper arrow: artif. sten.; lower arrow: pulm. valv. Left: frontal view. Right: side view.

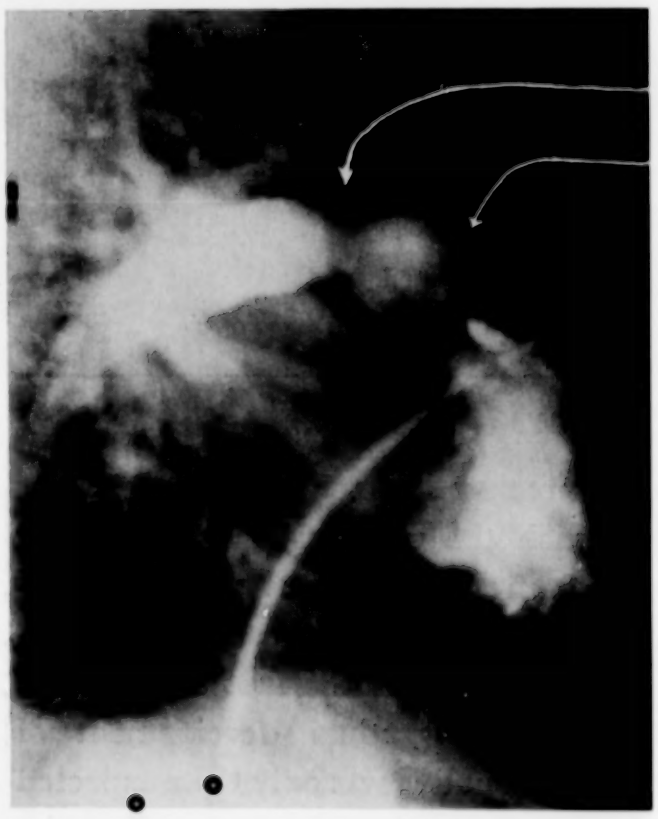
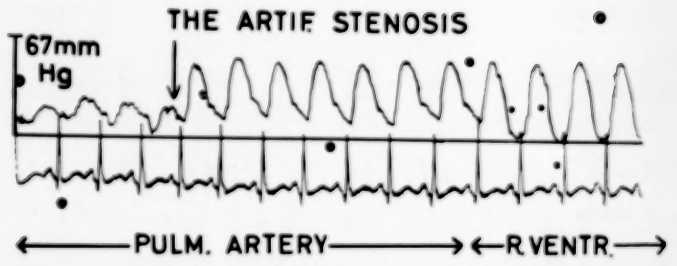


FIG. 4. *Ventricular septal defect.* Bente N., 6 months old. Dept. R, 4.10.55: Op. Dammann–Muller modified (only excision of a segment of pulmonary artery). (*a*) *Angiocardiography*, 3½ years postop. Upper arrow: artif. sten.; lower arrow: pulm. valv.



(*b*) Same patient, *pressure curve* at the cardiac catheterisation 3½ years postop.

ingly, it cannot be ruled out that progressive changes in the pulmonary vessels may have played a role. However, angiocardiography (Fig. 3) showed a pronounced hypoplasia of the pulmonary artery peripheral to the artificial stenosis, which provides weighty evidence in favour of the assumption that it is the artificial narrowing which had given rise to the development of a right-to-left shunt. Weighing against changes in the pulmonary vessels are also the facts that at the follow-up examination of

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Determination of Heparin Level of the Blood

Some Observations on Heparin Elimination and Correlation between Heparin Level and Clotting Time after Intravenous Injection

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The necessity of using heparin to prevent coagulation during extracorporeal circulation has made it desirable to have a method for controlling the heparin level of the blood. This applies particularly if a bleeding tendency appears during the postoperative course, when it is important to know whether or not the heparin has been adequately neutralized by protamine.

The method used for determination of the heparin content of the blood in connexion with such operations has been described and discussed earlier (Blombäck, Blombäck, Senning & Wallén, 1955 *a*, *b*) and is briefly given below. Furthermore, some observations on heparin elimination and correlation between heparin level and clotting time are reported.

In principle, the method is a thrombin titration. A constant amount of thrombin is added to plasma containing an excess of the heparin co-factor; the clotting time will then be a function of the heparin concentration in the plasma.

MATERIAL

1. *Human standard plasma.*—Blood from several donors is drawn into a solution of 3.7 % trisodium citrate ($\times 2H_2O$) (1 part citrate to 9 parts blood). The blood is centrifuged and the plasma samples pooled and frozen at −20°C in closed vials. Each vial should contain about 50 ml of plasma. Thawing of the plasma should take place rapidly at 37°C. During the determination, the plasma is kept at 0°C (ice-water).

2. *Bovine plasma (heparin co-factor).*—The bovine blood is drawn into 3.7 % citrate solution as described above. After centrifugation, the plasma is frozen in 50 ml portions at −20°C. Under these conditions the reagent is stable for at least some months.

After thawing the plasma is kept at 0°C during the determination.

3. *Thrombin.*—The thrombin is of bovine origin, and was usually prepared according to Seegers, Loomis & Vandenbelt (1945). The activity of this thrombin

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TABLE 1.

	Heparin, I.U./ml				
	0	0.4	0.6	0.8	0.98
Clotting time, sec.	14.5	20.1	28.2	44.5	70.0
	14.0	20.6	30.3	46.2	72.3
	13.5	19.0	28.5	48.3	77.0
Mean	14.0	19.9	29.0	46.3	73.1

TABLE 2.

	Heparin, I.U./ml			
	0	0.1	0.2	0.4
Clotting time, sec.	30.5	32.5	39.4	69.0
	30.5	32.5	39.4	68.9
	30.0	32.5	37.9	80.0
		32.5		79.0
				77.0
Mean	30.3	32.5	38.9	74.8

3–5 minutes, after which thrombin is added, and the clotting time determined as described above. Two or three determinations are made, and the mean value taken. The number of heparin units/ml of plasma is then read off on the standard curve. If desired, the plasma sample can be stored at −20°C before the determination.

If the clotting time of the sample is too high to be read off directly on the curve, the sample must be diluted with human standard plasma. Dilution with physiologic saline gives a deviating value, possibly due to the decrease in fibrinogen concentration of the system.

Since in principle the method is a thrombin titration the original thrombin concentration will, in fact, be decisive for the course of the curve. If the thrombin concentration is increased, larger amounts of heparin can be determined. If an increase in thrombin concentration gives a decrease in the clotting time for the zero point (sample without heparin), e.g. from 14 seconds to about 11 seconds, it implies that the heparin concentration must be increased by, in round figures, 30 % to obtain the same clotting times as for the lower thrombin concentration. In this way, higher heparin concentration can be determined within the same clotting time range.

As can be inferred from Table 1, the first part of the curve in the case in question, corresponding to a heparin concentration of less than 0.4 I.U./ml, is somewhat flattened. Consequently, the determination in this part of the curve cannot be as exact as in its steep part. If it is desired in this case to determine exactly an activity below 0.4 I.U./ml, the original thrombin solution must be diluted. With a thrombin solution containing approximately 2–3 N.I.H. units/ml, the zero point of the standard curve will lie between 25 and 30 seconds. A heparin activity between 0.1 and 0.4 I.U./ml can then be determined (see Table 2).

RESULTS AND DISCUSSION

The technique described is simple and rapid. It takes less than 10 minutes to determine the heparin level of the plasma. Moreover, as far as the ordinary commercial brands of heparin are concerned, the thrombin method has shown good agreement with the whole-blood method according to Jalling, Jorpes & Lindén (1946), and the method has been found reliable for determination of ordinary commercial heparin injected into the blood stream. Furthermore, very

is about 80 N.I.H. units/mg. Commercial brands of thrombin, e.g. Topostasin Roche or Thrombin Topical (Parke Davis), were also used. The thrombin is dissolved in distilled water to a strength of 40 N.I.H. units/ml. The solution is frozen in 20-ml portions and can be stored at −20°C for several weeks. For the determination, the thrombin solution is diluted with distilled water, so that the clotting time for the zero point of the standard curve will be 14–15 seconds. The reagent diluted in this way is kept in silicone-treated glass vessels at 0°C, and then remains unchanged for several hours (at most 6–8).

4. *Heparin.*—Heparin Vitrum, containing 100 I.U./mg, is used. For the standard curve a stock solution in 0.9 % NaCl, containing 20 I.U./ml is prepared and stored frozen at −20°C. For injection, 5 % Heparin Vitrum (5000 I.U./ml) was used.

5. *Siliconization* was performed with Siloxan 300 (Uddeholmsbolaget, Sweden).

PROCEDURE

Five ml of standard human plasma is pipetted into each of five test tubes. To the first tube is added 0.5 ml of 0.9 % sodium chloride. Heparin in a rising series is added to the other tubes, and the volume added then adjusted to 0.5 ml with physiologic saline. The quantity of heparin should be adjusted to give the following final activity in the standard series: 0, 0.4, 0.6, 0.8 and in the fifth tube 1.0 I.U./ml of plasma mixture (volume 5.5 ml). The contents of the tubes are well mixed.

Into each of 3 clean test tubes (10 × 80 mm) is pipetted in the following order: 0.5 ml of bovine plasma, 0.5 ml of distilled water and 0.5 ml of normal plasma (first tube in the standard series). The tubes are then placed in a water bath at 30°C, and incubated for 3–5 minutes. Using an ordinary tuberculin syringe, 0.5 ml of thrombin solution is added to one tube at a time, and a stopwatch started simultaneously. The end-point of the clotting time is given by the first fibrin threads picked up by a looped platinum wire, which is moved cautiously up and down in the tube during the determination. When the clotting time for all three tubes has been noted, similar determinations are made on the standard plasma, containing 0.4, 0.6, 0.8 and 1.0 I.U./ml of heparin, respectively. A typical series is shown in Table 1. The longest clotting time should not be much longer than 100 seconds, as the fibrin threads then become extremely fine and difficult to detect.

A standard curve can be plotted by using the mean value for the clotting times on the ordinate, and the corresponding heparin concentration on the abscissa. It has a typical exponential course. This curve has to be redrawn each day or as soon as a new thrombin sample is thawed.

The blood of which the heparin concentration is to be determined is withdrawn into 3.7 % sodium citrate (1 part to 9 parts blood). The blood is centrifuged for at least 4–5 minutes at 3000–4000 *g* and the plasma pipetted off. To a test tube is added 0.5 ml of bovine plasma and 0.5 ml of distilled water, as well as 0.5 ml of the plasma to be tested. Incubation is performed for

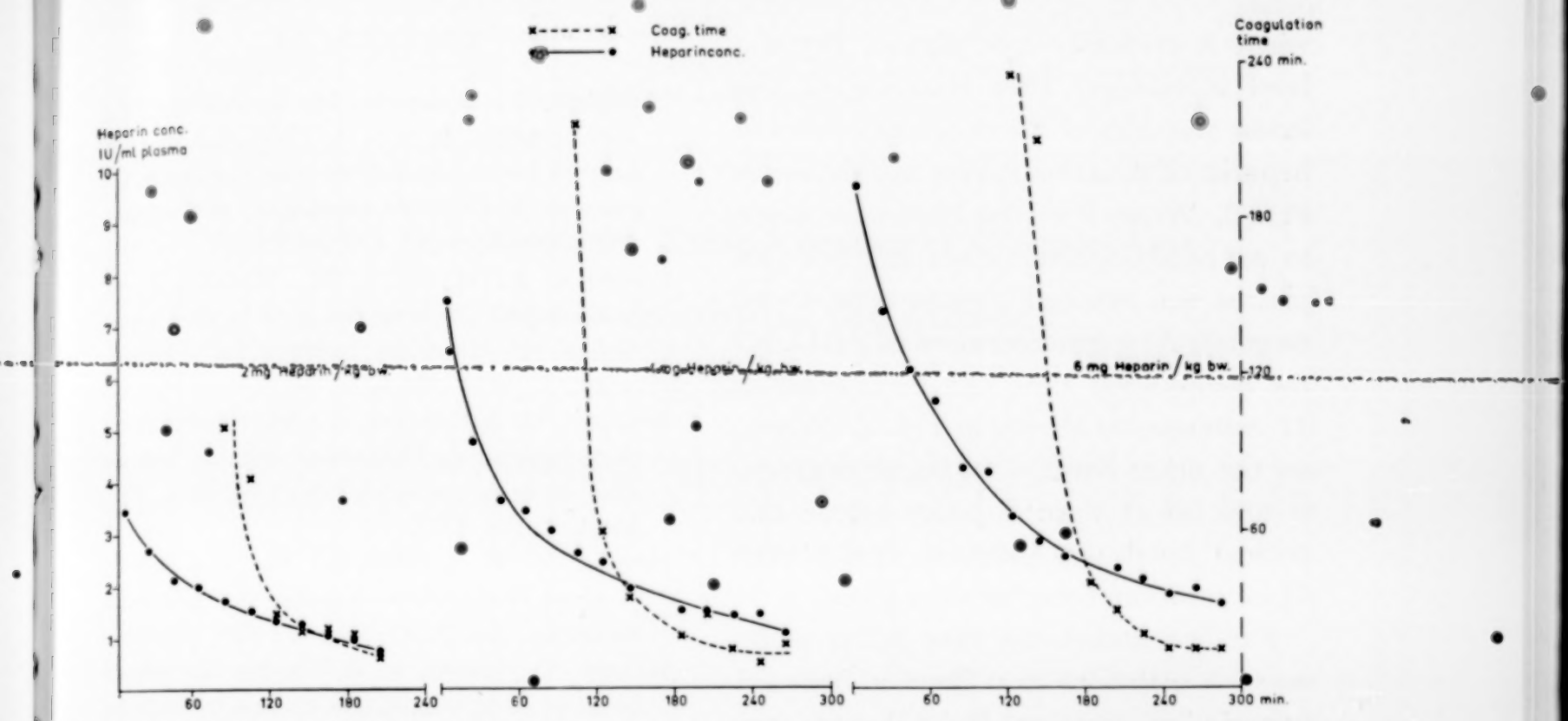


FIG. 3. Heparin elimination after injection and its correlation to coagulation time. Heparin concentration in I.U./ml plasma. Time in minutes.

sence of an excess of co-factor has proved to have good reproducibility. With this method, heparin added to the fresh plasma of different individuals can be recovered to 108 ± 4 %, as compared to that recovered after addition to the thawed standard plasma. Since the standard plasma has been frozen, and the sensitivity to heparin thereby reduced, the amount recovered will lie a few per cent above the expected amount. This error is decreased when the sample is diluted with standard plasma, and it is obviously eliminated when also the sample has been kept frozen.

From the clinical point of view, it is of importance to ascertain the correlation between the biological effect of heparin and its plasma concentration. Intravenous injections ranging from 2–6 mg/kg b.w. (200–600 I.U./kg) were given to 10 patients, and the heparin concentration and the corresponding clotting time at various intervals were determined after injection. The clotting time was determined with a modification of Bergquist's method (Jorpes, Blombäck & Blombäck, 1954) when the coagulation time was less than 20 minutes. Samples with longer coagulation times were determined in test tubes. Like Jaques (1939) and Monkhouse (1953), we found the individual variation in clotting time at a given heparin concentration to be very great (Fig. 2). For example, at 1.2 I.U./ml, the coagulation time varied between 17 and 110 minutes, and at 2.5 I.U./ml it varied between 40 minutes and no coagulation within 12 hours. At a concentration of more than 3.6 I.U./ml no coagulation occurred within 12 hours.

It is also important to know the elimination of heparin to get an idea of

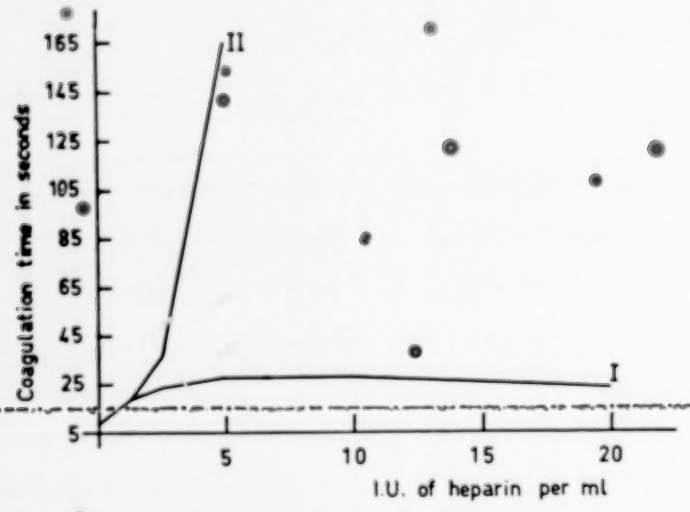


FIG. 1. Correlation of clotting time to plasma heparin concentration in a thrombin-plasma system. I, Human plasma; II, human plasma + bovine plasma.

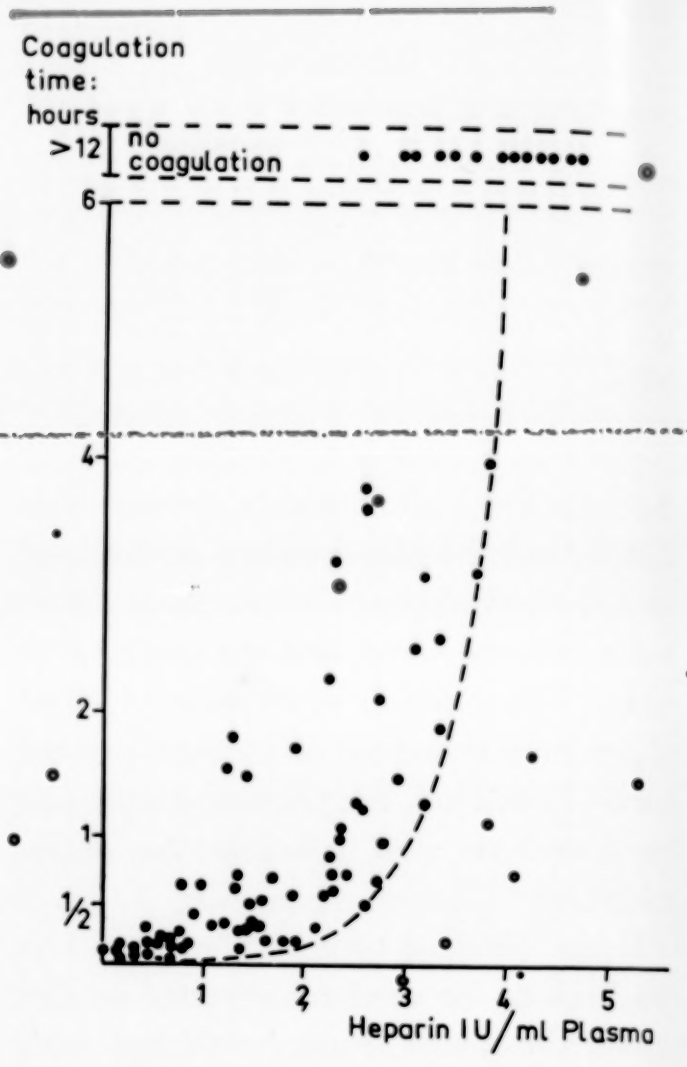


FIG. 2. Plasma heparin concentration in I.U./ml correlated to coagulation time.

small quantities of heparin can be determined with this method (1–2 γ/ml above normal). Several other techniques have been described in the literature; an account of them has been given earlier (Blombäck, Blombäck & Wallén, 1955; Blombäck, Blombäck, Senning & Wallén, 1955).

During the preliminary attempts to elaborate the method in question, we added varying amounts of heparin to human plasma *in vitro* and determined the clotting time after addition of thrombin. It was, however, found with respect to human plasma that, in most cases, an increase in heparin concentration above 1.5 I.U./ml no longer produced the expected exponential prolongation of the clotting time. If bovine plasma is added to human plasma, the sensitivity to heparin is greatly increased (Fig. 1). Moreover, there is also a considerable variation between the plasma of different individuals. After addition of bovine plasma, this difference is reduced.

The increase in sensitivity at high concentrations of heparin that is produced by addition of bovine plasma is due to the fact that the latter has a higher content of a factor necessary for the heparin effect. It was already shown by Howell & Holt (1918) that the action of heparin in a thrombin-fibrinogen system requires the presence of a co-factor found in plasma. In fact, the concentration of co-factor in human plasma is only about 20 per cent of that in bovine plasma. Species differences in co-factor concentrations as well as properties have also been observed by other workers (Burstein & Guinand, 1953; Magnusson & Nilsson, 1957).

The method described for determination of the heparin content in the pre-

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A Plasma Substitute in Extra-Corporeal Circulation: An Attempt to Minimize the Damage to the Blood

A Preliminary Experimental Report

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Since the advent of extra-corporeal circulation, efforts have been made to minimize the damage done to the blood elements by the methods and machines used. Machines, in particular, have been devised that are less injurious to the red cells and the plasma proteins. Siliconizing and other technical methods have been used to decrease trauma to the blood. An alternative approach would be to avoid using the patient's blood at all during the perfusion. This could be accomplished by withdrawing the patient's blood at the beginning of the perfusion and using donor blood or a blood substitute instead. At the end of the perfusion the donor blood or blood substitute could be withdrawn from the patient and the autologous blood returned to the patient.

The following is a report of preliminary experience with the use of a plasma substitute containing washed red blood cells for total body perfusion with extracorporeal circulation.

METHODS AND MATERIALS

The plasma substitute consisted of an isotonic Ringer solution containing Low Molecular weight Dextran in a concentration calculated to give a colloid osmotic pressure comparable to that of normal plasma. To avoid hypoglycemia, glucose was added and as an aid to the buffering power of the hemoglobin, one-half the calculated dose of $NaHCO_3$ as suggested by Ito *et al.* (1) was also added. The composition of the solution was as follows:

1. Ringer solution. NaCl = 0.9 g/100 cc; CaCl = 0.024 g/100 cc; KCl = 0.042 g/100 cc.
2. Low Moecular Dextran: 2 g/100 cc.
3. Glucose: 0.1 g/100 cc.
4. $NaHCO_3$ (Calculated to 2 mmEqv/kg body weight).

The Low Molecular weight Dextran used (Pharmacia, Uppsala) has an intrinsic viscosity of 0.16.

To this solution was added washed red cells, spun down from fresh heparinized dog donor blood, to a hematocrit of 40 %.

when a critically low plasma heparin level is reached after injection of different amounts of the drug. Examples of heparin elimination curves are shown in Fig. 3. When 2 mg/kg b.w. were given to an adult, a level of about 2 I.U./ml plasma was reached already after 45–60 minutes. At a concentration of 2 I.U./ml the coagulation time can be as short as 12 minutes, as shown in Fig. 2. When, on the other hand, 4 mg/kg were given, it took more than 2 hours before this critical level was reached, and almost 4½ hours when 6 mg/kg were given.

Further studies are now being made on such questions as difference between heparin elimination in different age groups, and at different body temperatures.

SUMMARY

A method is described for determination of the plasma concentration of heparin. It is primarily intended for use in connexion with operations using extracorporeal circulation, in which heparinization is necessary. In principle the method is a determination of the clotting time as a function of the heparin concentration, in a system with a constant amount of thrombin and an excess of heparin co-factor.

Some observations on the heparin elimination from plasma and on the correlation of heparin level to coagulation time are reported.

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TABLE 1. Experiment 2, laboratory data.

pO_2	pCO_2	pH	Bic	Na^+/S mequ.	K^+/S mequ.	Ca^{++}/S mequ.	Cl^-/S mequ.	P/S mg %	Total proteins %	Blood sugar	Fibrinogen %	Hb %	RBC (mill.)	WBC
						Pre-perfusion. Anaesthesia								
62.6	19.3	7.56	18.1	142	3.0	5.6	118	0.5	6.1	0.08	0.27	103	5.1	6000
						Perfusion period 20 min.								
293.1	20.2	7.30	11.0	141	3.3	2.8	120	0.7	1.4	0.51	0.04	71	4.2	2100
337.4	20.5	7.32	11.4											
						3 hours post perfusion								
			13.0	144	2.0	3.6	—	1.3	3.3	0.27	0.11	72	3.9	1600

normal value). The animal demonstrated no neurologic deficit. The pre-perfusion pH of the artificial plasma–red cell suspension was 7.5 and post-perfusion pH of the dog's own blood was 7.6. (3 hours post-perf.)

Bleeding from the operative incisions was not a problem during the perfusion in spite of absent blood clotting elements. Nor was there any undue postoperative oozing. Polybrene was used to counteract heparinization. The dose was between 1.5 and 1.8 times the previously administered heparin. This drug has been well tolerated when administered slowly in dilute solution and its antiheparin effect seems more effective than that of protamine; confirming the observations of Weiss *et al.* (5) in January 1959.

Experiment 2

To further demonstrate the feasibility of total body perfusion utilizing a completely synthetized liquid vehicle to increase the suspension stability of the red cell solution, a second experiment was performed on a 10 kg animal, extending the perfusion time to 20 minutes.

Procedure.—The perfusion carried out here was similar to the first experiment in all details including the low arterial perfusion pressure and normal EEG and ECG.

Result.—This dog also survived the acute experiment, awakened and demonstrated his neurological intactness by whining and other voluntary movements of his head and all extremities. The animal succumbed suddenly 30 hours after the perfusion. Autopsy disclosed a massive hemothorax arising from a technically unsatisfactory suture line in the right atrium. The laboratory data obtained are presented in Table 1.

This last experiment is not considered entirely valid even though the animal survived the acute experiment and seemed grossly intact neurologically. Survival time was too short to permit critical evaluation.

DISCUSSION

The first experiment has clearly demonstrated the feasibility of using a plasma substitute–red blood cell suspension for total body perfusion during extracorporeal circulation. The use of such a blood substitute may have two advantages. First, the patient's own blood is spared the trauma of circulating

The machine used for the perfusion was the De Wall–Lillehei (2) oxygenator with sigmamotor pumps. The only change in the apparatus was the incorporation of the disposable stainless steel filter manufactured by Abbott. The machine was primed with an amount of synthetic blood equal to the usual amount of blood used for perfusion plus 1200 cc extra.

Experiment 1

A 12 kilogram healthy mongrel dog was anaesthetized with intravenous Sodium Penthothal in small intermittent doses after premedication with morphine sulfate (24 mg) and 1.5 mg atropine sulfate. Room air was administered by a mechanical respirator via an endotracheal tube.

A right thoracotomy was performed and the azygos vein ligated. The animal was heparinized with 1.5 mg of heparin per kilogram body weight. Venous cannulae were inserted in the superior and inferior caval veins via the right auricle and the arterial cannula was placed in the left femoral artery. The perfusion was started, utilizing a flow rate of 100 cc per kg body weight and the animal was put immediately on complete bypass.

The first 1200 cc of blood returned from the venous line were diverted to a siliconized container. After 1200 cc had been diverted (estimated blood volume of the animal) the venous return was redirected to the pump oxygenator. The animal was monitored by recording venous pressure, arterial pressure, electroencephalogram, electrocardiogram and body temperature. The perfusion was discontinued by again diverting the venous return of the artificial blood to another container while the helix reservoir was allowed to empty. The animal's own blood was then poured into the helix reservoir, having been partially oxygenated during the perfusion by exposure to an O_2 atmosphere. As the last of the animals' own blood was pumped into him, the machine was stopped and the occlusive tapes around the caval veins were immediately released.

Results.—Pre-perfusion tracings demonstrated normal EEG, ECG, and rectal temperature of 37°C. Venous pressure varied between plus and minus 3 mm Hg. Arterial blood pressure registered 110 systolic over 70 diastolic in mm Hg. During the ten-minute perfusion, the ECG and EEG remained normal. Venous pressure rose slightly at the beginning of the perfusion but never exceeded 3 mm Hg. Rectal temperature fell 1°C. The arterial blood pressure decreased to between 30 and 40 mm Hg, when the perfusion was started and remained there throughout the perfusion. It returned to pre-perfusion levels when the perfusion was over and even rose above pre-perfusion levels to 130 mm Hg.

Postoperatively, the animal was given 50 cc of fresh citrated donor blood to replace the loss via intercostal catheters. The animal was given 5 mg intravenous N-allyl-nor-morphine to hasten awakening time. Full consciousness was regained three hours after the perfusion was discontinued. The animal is alive and well one month postoperatively. The postoperative hematocrit, 36 hours after surgery was 22 %, hemoglobin 47 % and red cell count 3.3 mill. per cc. The total serum proteins were 5.4 % (low

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The Clinical Use of a Screen Oxygenator (Mark III) in Closure of Atrial Septum Primum Defects

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The ideal extracorporeal perfusion should be able to maintain the circulation during open cardiotomies in such a way that the physiological status of the patient is not reduced more than what is due to anaesthesia and surgery. When the perfusion answers this demand, the repair of simple malformations such as atrial septum primum defects should not carry a higher mortality than do similar operations by closed methods.

In this clinic atrial septal defects of the secundum type have been satisfactorily closed by the Søndergaard circumclusion method or when anomalous pulmonary veins were present by atrio-septopexy as described by Bailey. A follow-up study of the first 70 cases operated by closed methods has been published by Davidsen.

None of the closed methods are suitable for the correction of the septum primum defects. When such defects have been diagnosed preoperatively, operation has been postponed until open repair could be undertaken during extracorporeal circulation.

MATERIAL

In nine patients atrial septal defects have been closed while the circulation was maintained by a screen oxygenator (Mark III) built after the Gibbon principle by the Mark Company.

Eight patients had simple septum primum defects. One of them had a valvular pulmonary stenosis as well. One patient, a 46-year-old man who was in severe congestive failure prior to surgery, had a secundum defect, a mitral stenosis and incompetence of the aortic and tricuspid valve. He was operated on as a salvage case and was the only patient who did not survive.

THE PUMP OXYGENATOR

The oxygenator consists of 16 stainless steel screens each 35 cm high and 40 cm wide giving a total area for the blood film of 4.5 sqm. The blood is drained by gravity from the patient to the apparatus. The two pumps are of the DeBakey type. One of them maintains the internal circulation in the apparatus, the other re-

through the pump-oxygenator. However, this same advantage can be obtained by using donor whole blood rather than a blood substitute. The second advantage of using a blood substitute seems to be of more importance, namely that it may be possible to devise a blood substitute which is more efficient than whole blood in oxygen transport. Interest in low molecular weight dextran, at this Institute as a means of maintaining circulatory efficiency under various adverse conditions prompted investigation of this plasma substitute in extracorporeal circulation (3, 4). Following burns, fractures, hypothermia and other forms of trauma intravascular aggregation of red blood cells or "sludging" has been observed by many investigators. When intravascular aggregation occurs, blood flow slows down. This has been correlated with a reduced suspension stability of the blood. The infusion of low molecular weight dextran solutions to patients and experimental animals with intravascular aggregation has caused the aggregation to disappear and blood flow to improve. This ability of low molecular weight dextran to improve blood flow may be useful in total body perfusion via extracorporeal circulation. The fact that the animals in these experiments maintained normal ECG and EEG patterns in spite of an arterial pressure in the range of 30–40 mm Hg may indicate a more efficient oxygen transport via plasma substitute–red cell suspension. The work of Gelin would indicate that this was due to a decreased viscosity and increased suspension stability of the blood.

This work is obviously of a preliminary nature. Further investigation will be required to critically evaluate the use of a plasma substitute in extracorporeal circulation. It seems likely that a more efficient circulation might be obtained by using a mixture of whole blood and low molecular weight dextran, rather than a dextran–red cell suspension. Further experiments to determine the optimum quantity of low molecular weight dextran required to produce optimum suspension stability of the blood are in progress.

SUMMARY

1. The case report of a successful, short-time, total body perfusion in a dog with a heart-lung machine utilizing a plasma substitute–red blood cell suspension is presented.

2. A method of sparing the animal's own blood from use during the perfusion is described.

3. The potential application and value of the use of this method is discussed.

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TABLE 1

Case no.	Sex, age (yrs.)	Weight (kg)	Surface area (sqm)	Function group	Defects	Remarks
1	M, 14	54.5	1.55	1	Primum	No complications
2	M, 6	19.5	0.79	2	Primum	No complications
3	F, 21	54.0	1.60	1	Primum	No complications
4	M, 23	71.5	1.83	2	Primum	Bacterial endocarditis, cured after 2 months. (Previous attempt of circumclusion operation)
5	F, 8	31.4	1.03	2	Primum Valv. pulm. sten.	Right lower lobe pneumonia
6	M, 44	75.1	1.97	3	Secundum Mitral sten. Aortic incomp. Tricusp. incomp.	Died
7	F, 34	52.2	1.61	2	Primum	Right lower lobe pneumonia
8	F, 13	46.8	1.48	1	Primum	No complications
9	F, 10	30.1	1.11	1	Primum	No complications

of the catheters are placed in the central vessels. The right femoral artery is dissected out below the ligament to be ready for cannulation. The patient is turned on the left side and the operation is carried out through a right-sided thoracotomy.

When the pericardium has been opened and tourniquets are placed around the venae cavae intrapericardially, the patient is heparinized with 2.5 mg of heparin per kg. Then the arterial cannula is placed in the femoral artery and connected to the arterial line of the machine. Flexible polyethylene catheters with a hardened tip are used for cannulation of the venae cavae through the auricular appendage.

As soon as the catheters are in position partial perfusion is begun. When after some minutes the extracorporeal circulation is stabilized, the venae cavae are occluded and the atrium is opened. All the defects have been closed with interrupted stitches of 00 Deknatel silk without the use of a prosthesis. Upon closure of the atrial incision, partial perfusion is maintained for some time until the arterial pressure is stable at about 100 mm Hg and the venous pressure approaches the pre-perfusion level.

Protaminsulphate, 3.75 mg per kg, is given over a period of some minutes, immediately after the venous catheters are taken out and before the arterial cannula has been removed and the artery is repaired. It is convenient to do this while the coagulation time becomes normal, so oozing from the thoracic field has stopped before the chest is closed.

Hitherto we have not experienced any trouble regarding the haemostasis.

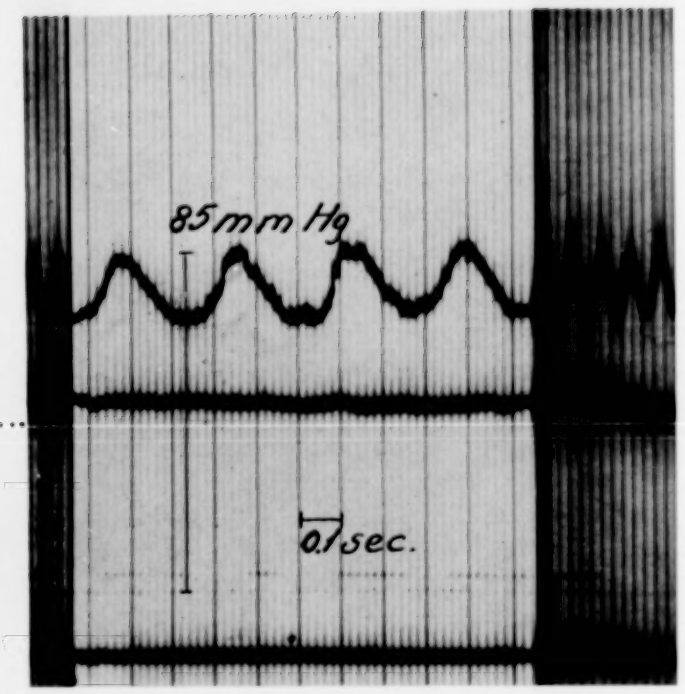


FIG. 1. Case no. 5. Aortic pressure curve during total perfusion at a rate of 3000 ml/min.

turns the arterialized blood to the patient. Both pumps work on ½-inch Tygon® tubes, which are used through the whole system. The DeBakey pumps give a low amplitude pulsatile flow. At an arterial flow rate of 3 liters per minute an amplitude of 18 mm of mercury has been measured in the abdominal aorta of a patient (Fig. 1).

Between each run the Lucite® and stainless steel parts of the machine are freed from deposits of organic material by 20 % sodium hydroxide, while the Tygon® tubes are renewed each time. Immediately prior to the perfusion the machine is sterilized by means of a 1.25 % Varexin® solution which is held in the assembled system for two hours. Cultures taken from the saline during rinsing of the machine have not given bacterial growth and no pyrogenes have hitherto been found. The machine including all extracorporeal tubing requires a primary volume of 2.8 liters of blood. The blood is drawn less than four hours before the perfusion into siliconized bottles containing 20 mg of heparin in 25 ml of a 25 % glucose solution for each 500 ml of blood. Two million units of penicillin and 1 g of streptomycin are added to the system at the priming.

Blood from each donor is cross-matched against the patient's blood; but no cross-matching is done between the donors.

ANAESTHESIA

After premedication with morphine and atropine, anaesthesia is induced with Narcodorm® (= Enibolmalnatrium N.F.N.) and succinylcholine. Anaesthesia is maintained with nitrous oxide, pethidine and Relaxan® (= Gallamoni jodidum N.F.N.). As the time for extracorporeal circulation approaches, the nitrous oxide is gradually withdrawn and the anaesthesia is maintained by refractive doses of pethidine. In this way the inconvenience of giving a massive dosis of barbiturate can be avoided at the time when the nitrous oxide must be cut off.

After the perfusion the patient is kept anaesthetized with nitrous oxide and Relaxan®. This is continued after the operation until the patient is rewarmed to about 36.5°C, which usually takes two hours. When prostigmine is given to reverse the neuromuscular block and the nitrous oxide is withdrawn the patient wakes up after two to four minutes.

OPERATION

When the patient is anaesthetized, catheters for pressure registration are introduced through the left femoral artery and left saphenous vein. The tips

TABLE 2

Case no. ...	1	2	3	4	5	6	7	8	9
Hb, %	94	90	92	103	95	90	99	87	86
Arterial O_2 saturation	99	99	95	92	99	88	83	97	99
Venous O_2 saturation	82	80	72	76	80	70	65	80	—
A – V diff., vol. %	2.9	3.2	3.9	3.0	3.2	3.0	3.3	2.7	—
Flow rate, ml/min.	4200	2850	5600	4600	3800	4500	4750	3500	4400
O_2 consump., ml/min.	139.2	91.2	218	138	121.6	135	156.8	94.5	—
Flow rate, ml/sqm/min.	3100	3600	3500	2500	3700	2300	3000	2400	4000
O_2 consump., ml/sqm/min.	90	115	136	76	118	70	97	64	—
Temp., °C	34.2°	34.1°	34.5°	35.2°	35.7°	34.3°	33.2°	33.7°	32.2°

mean of 90 mm Hg. In all cases the pressure in the inferior vena cava has been slightly or moderately elevated. In one case (Case no. 4) it rose gradually during the perfusion to 50 cm of water. In this patient, who weighed 71.5 kg, the venous catheters which had an internal diameter of 5.5 mm were obviously too narrow to secure a good venous return, and during the 10 minutes of caval occlusion the patient was greatly overtransfused in order to keep the flow rate at 2.6 l/sqm/minutes.

It seems now to be generally accepted that the ideal perfusion flow should be no less than the cardiac output during anaesthesia in order to avoid hypoxia and metabolic acidosis (Engell, 1956).

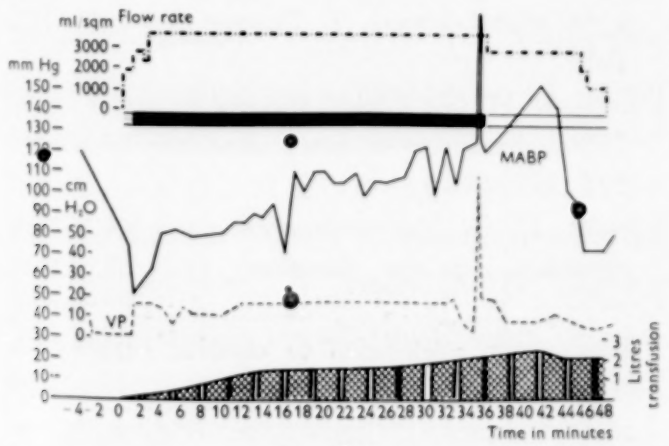


FIG. 6. Case no. 5. The acute rise in blood pressure at the end of the total perfusion period is due to light anaesthesia and coughing. The blood pressure drops temporarily at the end of the partial perfusion as 400 ml of blood are withdrawn from the overtransfused patient.

In earlier years, discussions about the ideal flow rate focused on the oxygen supply of the organism. Less interest has been paid to the fact that a deliberately chosen low flow can be established in two ways only, either by creating a venous stasis or by reducing the blood volume of the organism. None of these procedures is consistent with physiological principles.

As will be seen from Table 2, the arterial oxygen saturation has been below 90 % in two cases. In case no. 6, a man of 76 kg weight, the oxygenator has possibly been taxed close to the limit of its capacity. The arterial oxygen saturation was 88 %, the oxygen consumption of 135 ml/min. however was not as high as seen in some cases (Table 2). Presumably two of the screens have touched each other creating an "atelectasis" where blood not exposed to oxygen has flowed over the screens. The same incident might have caused the arterial oxygen saturation of 83 % in case no. 7.

The moderate "metabolic" acidosis during the perfusion is mostly due to the low standard bicarbonate of the donor blood. Thus it is not of the same consequence as a metabolic acidosis due to anoxia of the perfused organism would be (Fig. 7).

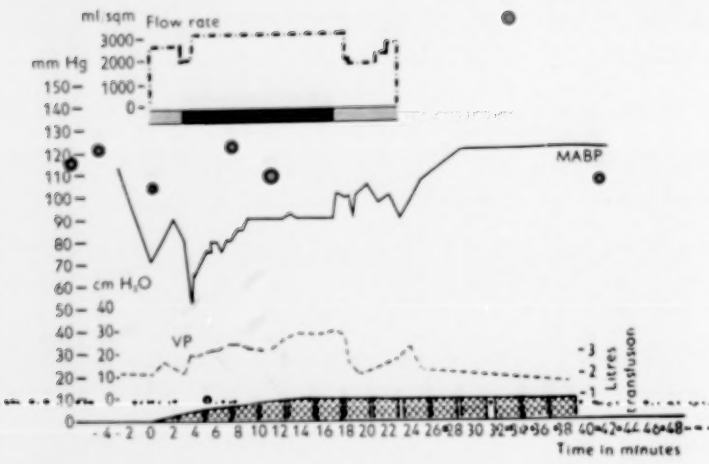


FIG. 2. Case no. 1. Flow rate and arterial blood pressure (solid line) dropped on caval occlusion (solid black). Flow rate went up before blood pressure during transfusion from the machine. Venous pressure (broken line) slightly elevated during total perfusion, drops when the caval tourniques are released.

PERFUSION

It has been our general principle to adjust the flow rate after the venous return from the patients, when they can be considered to have a normal blood volume. A flow rate about 3000 ml/sqm/minute is thought to be satisfactory.

When partial perfusion starts, the clamp on the venous line is slowly released in the course of some seconds, while the arterial pump is gradually speeded up, the blood volume being kept constant all the time by manual control. When the partial perfusion is well stabilized at a flow of approximately 2000 ml/sqm/minute the tourniques are tightened around the venae cavae and total perfusion is begun.

As will be seen from the graphs (Figs. 2–6) the total perfusion flow is fairly stable around 3000 ml/sqm/minute. The blood pressure varies more, but keeps a

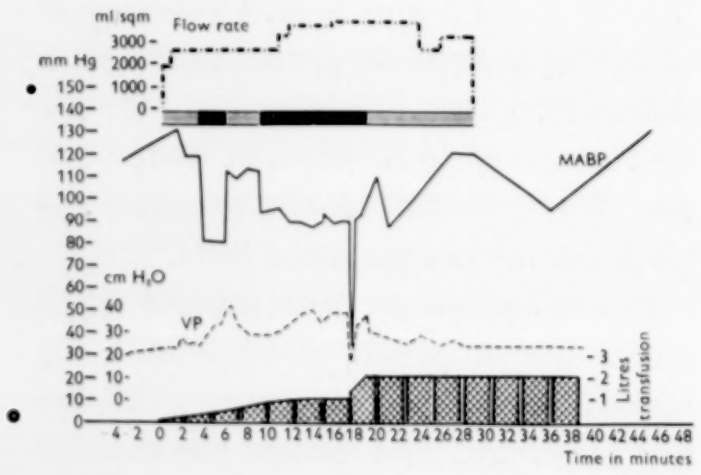


FIG. 3. Case no. 2. When haemorrhage occurred from the opened atrium this was temporarily closed with a clamp while blood loss was restored and the slack tourniquet—the reason for the haemorrhage—was tightened. The steep fall in arterial blood pressure later was caused by a disconnection of the arterial tube. The continuous pressure reading tells that the line was repaired and blood pressure restored in 15 seconds.

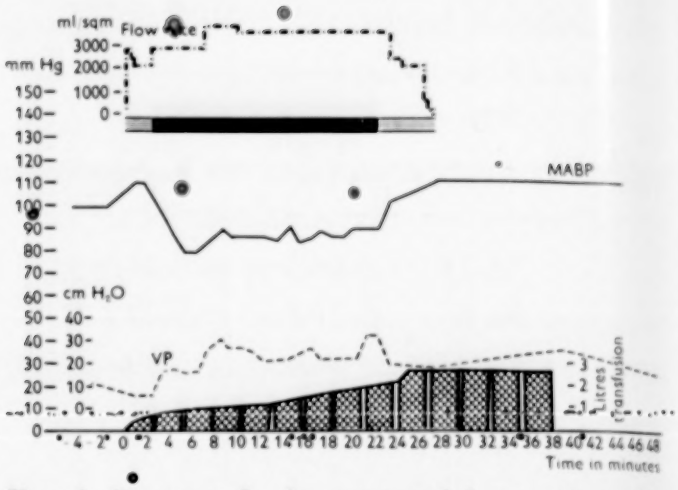


FIG. 4. Case no. 3. An uneventful smooth perfusion of a patient of 54 kg weight. The solid black indicates the caval occlusion period.

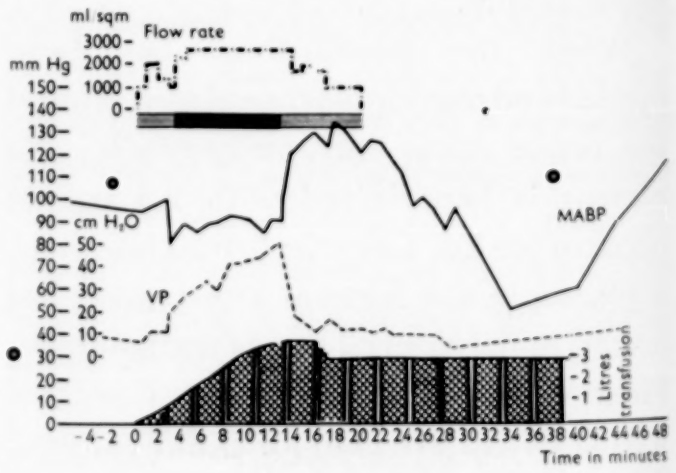


FIG. 5. Case no. 4. The venous catheters of 5.5 mm internal diameter were too narrow for this 71.5 kg individual. Flow rate could be kept only by overtransfusion and consequently venous stasis. At the end of the perfusion 900 ml of blood were drained back into the machine.

ACTA CHIRURGICA SCANDINAVICA, SUPPL. 245: 275–282, 1659

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A Study of Serum Enzymes during and after Open Heart Surgery with the Crafoord–Senning Heart-Lung Machine

Bo Norberg and Åke Senning

That cardiac necroses due to coronary obstruction result in the release of several enzymes leading to an elevation of the serum activity of these enzymes, with peak values between twelve and forty-eight hours after the obstruction or even later, is a well-documented fact (cf. e.g. Mason & Wroblewski, 1957; Hansen & Laursen, 1957; Hanson & Biörck, 1957). But traumatic injuries and surgical interventions may give rise to similar phenomena (Lieberman *et al.*, 1957; Hauss & Leppelmann, 1957; Schlief & Kamm, 1957; Albaum & Milch, 1957; Mignone *et al.*, 1955). Since cardiac surgery always involves an extensive operative trauma, especially in open heart surgery with extracorporeal circulation (ECC), it is of interest to know the pattern of serum enzyme changes in this connection. A study of the matter has accordingly been made and the results presented below indicate that the major enzyme changes appear immediately following the operation and subside rapidly in the next few days in uncomplicated cases.

MATERIAL AND METHODS

The material comprises 52 cases which have been described in an earlier communication (Norlander *et al.*, 1958) and five cases operated upon at Sabbatsberg Hospital, viz. 3 cases of atrial septal defect (one death), 1 tetralogy of Fallot, and 1 complete transposition of the great vessels (one death). In addition to this test group of 57 patients, a control group of 11 patients is included in the study. These patients had operations on the heart or the great vessels without ECC.

Samples were collected at varying intervals soon after the induction of narcosis and during surgery. After the operation a few samples were taken in the afternoon. During by-pass the samples were taken from the trough of the heart-lung machine*, and these are supposed to represent the mean composition in the whole vascular system. In a few cases samples were also taken in the tubings from the intracardiac suction devices before this blood entered the pool in the machine. Before and after ECC the samples were taken from an indwelling catheter in the radial artery.

* Manufactured by AGA, Lidingö.

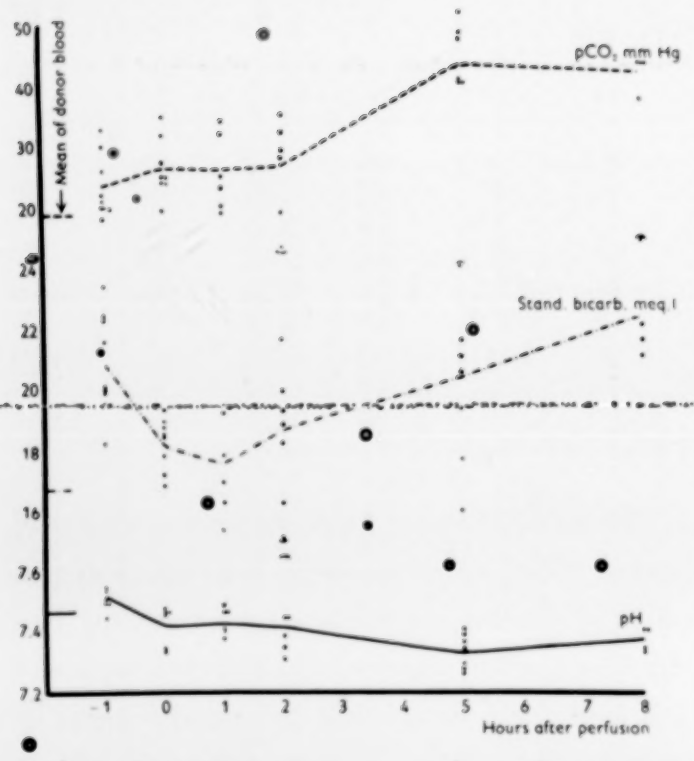


FIG. 7. The upper curve represents the mean values of pCO_2 during anæsthesia, at the end of perfusion (zero hour) and up to eight hours after the perfusion. The single points represent the individual cases. The middle curve represents the standard bicarbonate. The curve at the bottom gives the pH. The horizontal lines at the left indicate the mean values of the donor blood recirculated in the machine prior to perfusion.

POSTOPERATIVE COURSE

During the first 12 hours postoperatively the patients are observed in the recovery ward. It has been very useful to give assisted respiration by mask and bag for two minutes every quarter of an hour to all patients who are sufficiently cooperative. The effect of this procedure on alveolar ventilation has been proved by series of pCO_2 determinations on arterial blood. On smaller children tracheotomy is routinely performed after the operation. It is thought unwise to wait until stagnation of bronchial secretion and increasing pCO_2 makes tracheotomy mandatory.

Twenty-five hours after the operation anticoagulation therapy with dicumarol is started as a routine.

Of the seven patients who survived the operation, six have had a temperature between 39° and 40°C for two or three days. They all had a superficial phlebitis arising from the permanent drop catheter in the leg.

Two patients had a pneumonia in the right lower lobe. One patient developed an endocarditis with positive blood cultures of non-haemolyte streptococci. This was cured by prolonged treatment with antibiotics.

SUMMARY

During this first series of nine human extracorporeal perfusions for the repair of atrial septal defects the Mark III 16-screen oxygenator-pump has proved a dependable tool for intracardiac surgery in patients between 19 kg and 76 kg of weight, and a standard technique of perfusion and postoperative treatment has been established preliminary to attempts at correcting more complicated anomalies in this clinic.

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TABLE 2. Mean serum enzyme activities during the first part of the operation before ECC.

Relative activities. Number of samples in brackets.

Time before ECC	ALD	GOT	GPT	LD	MD	OCT
3 –2½ hrs.	112 (6)	60 (7)	22 (5)	74 (6)	99 (6)	68 (3)
2½–2 hrs.	139 (5)	51 (3)	18 (3)	68 (5)	92 (4)	— —
2 –1½ hrs.	115 (7)	54 (6)	13 (4)	75 (3)	145 (6)	49 (3)
1½–1 hrs.	115 (8)	54 (9)	26 (4)	83 (5)	85 (7)	39 (2)
60–45 min.	105 (3)	57 (4)	34 (1)	73 (2)	93 (8)	35 (1)
45–30 min.	123 (9)	54 (9)	18 (7)	74 (6)	94 (9)	68 (2)
30–15 min.	157 (6)	102 (8)	30 (6)	108 (6)	138 (10)	61 (1)
15– 0 min.	125 (17)	54 (26)	27 (9)	75 (12)	117 (29)	102 (4)

TABLE 3. Mean serum enzyme changes during the extracorporeal phase of the operation.

Relative activities. Number of samples in brackets.

Time (min.)	ALD	GOT	GPT	LD	MD	OCT
0–10	134 (25)	60 (29)	21 (15)	77 (16)	180 (29)	53 (11)
11–20	152 (29)	81 (39)	27 (18)	87 (19)	217 (37)	70 (9)
21–30	201 (27)	98 (31)	32 (16)	104 (15)	302 (33)	63 (8)
31–40	227 (21)	114 (22)	30 (10)	111 (14)	386 (26)	96 (7)
41–50	204 (9)	117 (14)	34 (4)	114 (3)	461 (13)	141 (3)
51–60	283 (5)	124 (5)	27 (4)	111 (5)	459 (8)	122 (4)
61–70	245 (3)	192 (3)	— —	126 (2)	581 (3)	— —
71–80	284 (2)	127 (2)	33 (2)	114 (1)	452 (2)	88 (2)
81–90	394 (3)	186 (3)	50 (2)	129 (2)	572 (3)	60 (4)

TABLE 4. Serum enzymes after ECC and up to the next morning.

Mean relative activities. Number of samples in brackets.

Time after ECC	ALD	GOT	GPT	LD	MD	OCT
0–15 min.	227 (15)	112 (19)	31 (8)	111 (12)	412 (22)	37 (1)
15–30 min.	242 (24)	140 (30)	38 (13)	114 (19)	423 (33)	67 (4)
30–45 min.	232 (15)	149 (18)	39 (8)	119 (11)	419 (19)	207 (2)
45–60 min.	261 (15)	160 (18)	38 (11)	113 (13)	457 (19)	66 (2)
1–1½ hrs.	308 (16)	166 (23)	35 (8)	111 (11)	464 (21)	129 (2)
1½–2 hrs.	287 (17)	203 (17)	40 (10)	129 (13)	619 (19)	111 (3)
2–2½ hrs.	401 (6)	153 (10)	42 (3)	130 (5)	583 (10)	58 (1)
2½–3 hrs.	271 (6)	208 (9)	38 (3)	125 (4)	652 (7)	22 (1)
3–4 hrs.	295 (5)	361 (7)	52 (2)	160 (5)	886 (7)	— —
4–5 hrs.	322 (4)	182 (5)	43 (4)	131 (2)	507 (5)	56 (1)
5–6 hrs.	361 (9)	296 (10)	45 (5)	150 (9)	635 (10)	59 (2)
6–10 hrs.	289 (12)	271 (15)	52 (12)	135 (10)	643 (13)	79 (5)
Next day	349 (32)	252 (41)	54 (22)	162 (25)	287 (40)	90 (8)

From the second day samples were taken daily in the morning for a week and later every other day if possible. In most of the children, however, the postoperative sampling was reduced, owing to the difficulties of getting sufficient amounts of blood.

Enzyme assays were performed on the same day whenever feasible, and in other cases the serum was separated as soon as possible and kept refrigerated until assayed.

Malic dehydrogenase (MD) and lactic dehydrogenase (LD) activities were measured as previously reported (Crafoord, Norberg & Senning, 1957). For glutamic oxalacetic transaminase (GOT), however, the Reitman and Frankel procedure was used in preference to the modified Karmen technique previously applied. Glutamic pyruvic transaminase (GPT) was assayed with the method analogous to GOT (Technical Bulletin No. 505, Sigma Chemical Co.). Aldolase (ALD) was assayed according to Beisenherz *et al.* and the ornithine carbamyl transferase (OCT) activity was measured as ammonia nitrogen liberated from citrullin on incubation in an arsenate buffer (Reichard).

When visible, hemolysis was estimated as mg % hemoglobin by measuring the oxyhemoglobin absorbance at 540 mμ in 0.007 *N* ammonia.

RESULTS

In order to facilitate the comparison of patients with widely differing ECC times, the extracorporeal phase is treated as an entity and the sampling time is counted in hours and minutes before the start of the by-pass, after which the time is counted from the end of the ECC.

TABLE 1. Normal ranges of serum enzyme activities.

Enzyme	Range: Regular units	Range: Relative units
Aldolase (ALD)	3–8	37–100
Glutamic oxalacetic transaminase (GOT)	8–30	27–100
Glutamic pyruvic transaminase (GPT)	5–35	14–100
Lactic dehydrogenase (LD)	140–290	48–100
Malic dehydrogenase (MD)	30–80	37–100
Ornithine carbamyl transferase (OCT)	0–6	0–100

Furthermore, since the units of enzyme activities differ considerably numerically, it was decided to use a unified relative scale where the *upper normal limit represents the value 100*. In Table 1 are given the normal ranges for the enzymes included in this study (as obtained from healthy blood donors).

Enzyme changes during surgery

During the preparative phase of the operation the enzyme values oscillate

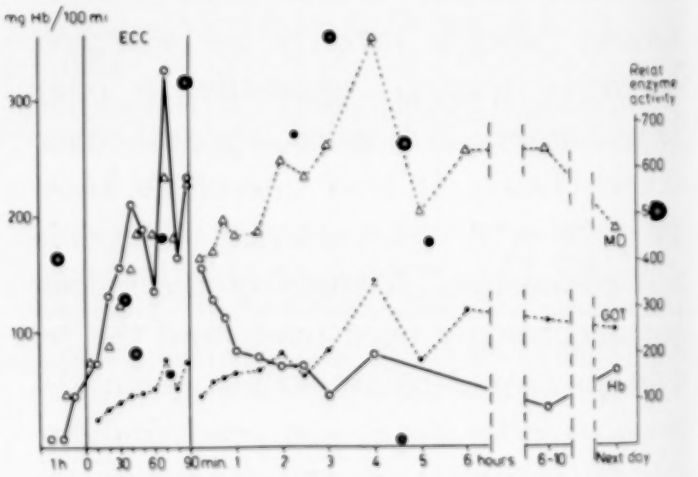


FIG. 1. Changes in plasma hemoglobin (circles and solid lines) before, during and after extracorporeal circulation, malic dehydrogenase (triangles, MD) and glutamic oxalacetic transaminase (solid dots, GOT).

within the normal range or slightly above it. This emerges clearly from Table 2.

The start of the ECC seems to induce a fairly rapid release of certain enzymes (Table 3), and at the same time hemolysis increases, as seen from Fig. 1. GPT and OCT, however, are unaffected or nearly so.

After the termination of ECC the hemolysis rapidly decreases (Fig. 1). but the enzymes, on the contrary, show a new upward course during several hours (Table 4), again with the exception of GPT and OCT.

In the control group five patients only were studied during the operation. The mean enzyme values are given in Table 5, and they show the same trend as in the preparative phase of the test group (Table 2).

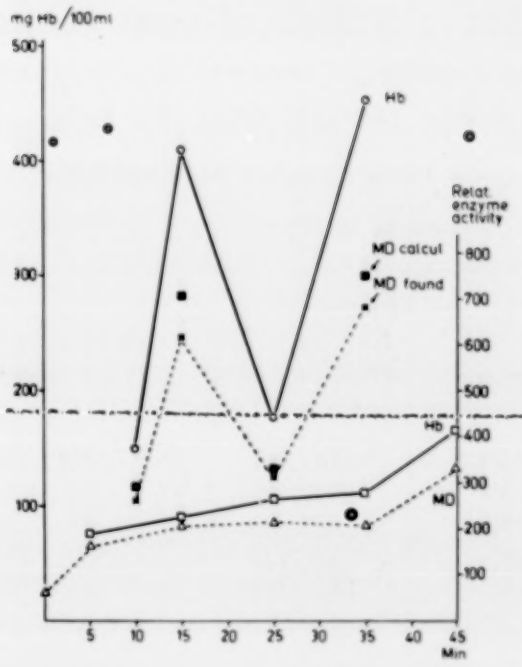


FIG. 2. Plasma hemoglobin during extracorporeal circulation. Lower solid line gives concentration in the trough of the heart-lung machine. Upper solid line shows the hemolysis in blood collected by suction in the open heart. The dotted lines show the corresponding MD values. Filled squares indicate calculated MD activities from the known difference in hemolysis and the average activity per 100 mg hemoglobin (Table 9).

Postoperative enzyme changes

The mean serum enzyme activities from the 2nd to the 14th day are presented in Table 6 for the test group and in Table 7 for the control group. In spite of the high enzyme values attained in the afternoon on the day of the operation for ALD, GOT, LD and especially MD, the second day already shows a definite downward trend for MD and essentially an unchanged level for the other three. In the course of the subsequent days all activities smoothly approach a normal level which is reached by the 14th day. This is also the case with the control group.

Three cases have been excluded from the main group in Table 6 on account of grossly abnormal behaviour, two from the second day and one from the third. Their serum enzyme values appear in Table 8. All three died within 24 hours after these samples.

DISCUSSION

The results seem to indicate that the increase in enzyme activities is due to the increased hemolysis during ECC. As a great deal of the hemolysis is caused by the suction devices, one may expect to find the changes exaggerated in the blood passing the tubings from the suction in the open heart. Separate sampling of this blood in 12 patients gave results confirming this expectation. Fig. 2 gives an illustration of this for malic dehydrogenase.

In order to see if the effect on all enzymes could be referred to hemolysis,

TABLE 5. Serum enzyme activities during and after operation in control cases.

Time, hrs.	ALD	GOT	GPT	LD	MD	OCT
		Relative values.				
Time of operation						
0–1	142	44 (4)	10	54 (2)	185 (3)	80
1–2	130	54 (4)	13	57 (2)	118 (3)	73
2–3	160	102 (3)	10	58 (2)	161 (3)	92
3–4		113				
4–5		99 (2)				
Time after operation						
0–1		47	11	70	113	93
1–2		134 (2)		69	200	
2–3		43			340	

TABLE 6. Relative serum enzyme activities during an uneventful postoperative course after open heart surgery.

Number of samples in brackets.

Days	ALD	GOT	GPT	LD	MD	OCT
2	349 (32)	252 (41)	54 (22)	162 (25)	287 (40)	90 (8)
3	280 (20)	267 (25)	72 (15)	168 (16)	278 (26)	41 (4)
4	268 (12)	208 (13)	88 (10)	148 (10)	268 (12)	37 (1)
5	192 (11)	188 (15)	81 (11)	164 (11)	186 (15)	40 (2)
6	170 (7)	153 (8)	42 (5)	170 (6)	187 (9)	90 (2)
7	180 (12)	139 (13)	99 (10)	153 (10)	146 (14)	94 (1)
8	147 (12)	131 (14)	81 (11)	134 (11)	161 (14)	106 (2)
10	178 (12)	115 (14)	68 (10)	148 (11)	147 (15)	—
12	112 (8)	113 (9)	59 (9)	141 (10)	110 (12)	64 (3)
14	80 (5)	52 (5)	52 (4)	120 (5)	127 (6)	35 (1)
36–30	116 (8)	96 (9)	74 (9)	107 (10)	128 (10)	48 (1)
61–44[a]	127 (3)	158 (3)	126 (3)	127 (3)	140 (3)	62 (2)
13–79[a]	143 (4)	117 (3)	74 (3)	103 (4)	80 (3)	120 (1)

[a] These values are from one patient who had an infection in this period. Eventually recovered.

TABLE 7. Serum enzymes in control patients.

Day	ALD	GOT	LD	MD
Preop.	156	36	89	77
1	146	45	75	107
2	—	70	114	146
3	242	69	130	165
4	—	—	105	139
5	270	103	123	146
6	—	129	114	159
8	181	131	100	90
10	134	60	104	99
14	62	70	119	97

TABLE 8. Postoperative enzyme values in three cases with fatal issue.

Day	ALD	GOT	GPT	LD	MD	OCT	Case no.
2	1220	945	1210	143	1190	2960	1
2	415	1030	151	284	1710	—	7
3	470	1135	364	300	1320	—	20

If one assumes the heart to be the main source of enzymes appearing in the blood after ECC, then cases in which the heart recovers poorly should give higher and longer increases. This seems actually to be the case, as appears from Table 8. Patient no. 1, however, also shows extremely high values for OCT and GPT, indicating serious liver damage. In this case it is impossible to decide whether liver failure or heart failure is the primary cause of death.

It has been stated that enzyme determinations in blood serum in connection with traumatic injury are useless as a diagnostic aid in suspected coronary infarction. When one considers the smooth postoperative decline in the serum enzymes reported here, it seems obvious that the enzyme changes characteristic of an infarction must be easily observed if this should happen after cardiac surgery.

SUMMARY

The serum activities of six enzymes in patients during and after open heart surgery with the heart-lung machine are reported. During extracorporeal circulation there is an abrupt increase in aldolase, glutamic oxalacetic transaminase and malic dehydrogenase, and a lesser increase in lactic dehydrogenase. This is to be explained as mainly due to the concomitant hemolysis.

After termination of the extracorporeal circulation a new increase in the serum enzymes appears, and this is probably due to release from the heart and to a smaller extent from damage to other tissues.

In an uncomplicated postoperative course the enzyme values go smoothly back to normal. Remaining high values or new increases signal complications and may therefore be of diagnostic or prognostic value.

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TABLE 9. Activity of some enzymes in hemolysates of washed erythrocytes and recovery of activities in mixtures of hemolysates and serum.

Number of experiments in brackets.

Enzyme	Mean activity at 100 mg % Hb (relative units)	Mean recovery in serum mixtures, %
ALD	23 (6)	95 (4)
GOT	83 (6)	58.5 (14)
GPT	51 (4)	34 (6)
LD	18 (13)	92 (14)
MD	161 (8)	89 (14)

washed red cells were hemolyzed with distilled water, and various amounts of hemolysate added to serum. Similar dilutions were made in saline, and both series were assayed for the different enzymes. The hemoglobin levels used were from 25 to 322 mg % Hb, but the values have been converted to 100 mg % Hb. They are given in Table 9.

The comparatively poor recovery of the transaminase activities remains to be explained. The aldolase recovery is good, but the total activity seems unexpectedly low as compared to published values (Sibley & Lehninger). We cannot rule out the possibility that low values were the result of low activity of the glyceraldehyde dehydrogenase and triosephosphatisomerase mixture (Boehringer) used in the assay procedure, as this was not checked. Some other of our experiments indicate such changes in the enzyme mixture. For comparison within the present series, however, this difficulty would hardly influence the conclusions. In consideration of the errors involved in the calculations the correlation between enzyme changes and hemolysis is reasonably good during ECC. It therefore seems justified to conclude that the main part of the increase in ALD, GOT, LD and MD during ECC is due to hemolysis.

After the end of the by-pass, however, this can hardly explain the increased serum enzyme activities, as the hemoglobin is going down at the same time. Theoretically, an increase in serum enzyme values from continued hemolysis without a corresponding increase in plasma hemoglobin would be conceivable if the hemoglobin clearance were much greater than the clearance of the enzymes. This requires the assumption that the hemoglobin clearance rate increases substantially after the ECC without a corresponding change in enzyme clearances. At present we have no evidence in support of this assumption. It therefore seems reasonable to assume that the enzymes are released from the injured tissues, and in the light of the known effects of anoxia on the heart it is probable that a good contribution comes from the heart in connection with incision, manipulation and suturing.

There is also the question of enzyme release from organs due to the general stress of the operation. It is known that major surgery provokes increased adrenal activity. And Schapira (1956) found an increase in serum aldolase and GOT after injections of desoxycorticosterone, in rabbits. Such a release would be generally distributed. However, GPT and OCT, enzymes which show increased values in liver damage, react very little. It therefore seems unlikely that any general stress effect is operative in the enzyme release after ECC.

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From the Thoracic Clinic, Stockholm, Sweden

Surgical Correction of Atrial Septal Defects

LENNART JOHANSSON and ÅKE SENNING

The Thoracic Clinic of Karolinska Sjukhuset has been partially open since April 1, 1957. It is our purpose to report on our experience of the surgical correction of atrial septal defects during the period of 23 months which have elapsed. The material comprises congenital defects, chiefly at the atrial level, irrespective of whether the defect was combined with other anomalies such as pulmonary valvular stenosis or anomalous pulmonary veins. Some patients have been operated upon by closed and others by open repair technique under hypothermia or extracorporeal circulation.

SURGICAL BACKGROUND

Various methods of surgery have been tried out for the closure of atrial septal defects. Attempts at repair have been made with the help of palpation inside the atrium. Cohn (1947) sewed a patch of the auricular wall to the defect, and Swan, Maresh, Johnson & Warner (1950) made a clinical repair by sewing the auricular appendage to the border of the defect. Bailey, Downing, Geckeler, Likoff, Goldberg, Scott, Janton & Redond-Ramirez (1952) used a similar method on a large clinical material, involving suture of the auricular wall to the border of the defect. They called this method atrio-septo-pexy. Schumacher, Moore & King (1953) performed experimental septo-pexy with a sac of pericardial or plastic material attached to the auricular wall. Hufnagel & Gillespie (1951) used a technique of attaching two nylon buttons to each side of the defect. The fact that different forms of plastic prostheses are well tolerated inside the heart and that they constitute suitable grafts has been demonstrated by several researchers. Donald, Kirklin & Grindlay (1953) used Ivalon sponge plugs. Miller, Gibbon, Greco, Smith, Cohn & Albritten (1954), Pomeranz, Watkins & Gross (1954), Bahnson & Baker (1953) all had good experience of different plastic materials.

Using Gross's "well" technique Kirklin, Swan, Wood, Burchell & Edwards (1955) operated on 59 patients with a mortality of three. In four of the first 53 patients a residual shunt was found postoperatively. In one of them the shunt was considered to be the same as before the operation. Later, in a series consisting of 120 patients with defects of secundum variety, the mortality rate was only 3 %, so that they continued

surgery with the Crafoord–Senning heart-lung machine. *Acta anaesth. Scandinav.*, *2*: 181, 1958.

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and has no posterocranial septal margin. Anomalous pulmonary veins often empty into the superior vena cava or its junction with the atrium.

2. OSTIUM PRIMUM DEFECTS. The defect descends towards the valvular plane, above which there is no septal tissue. The atrioventricular valves are intact.

3. OSTIUM ATRIOVENTRICULARE COMMUNE. The mildest cases have an atrial septal defect, cleft mitral or tricuspid valve, or defect in annulus fibrosus, more severe cases have a ventricular septal defect.

4. CORONARY SINUS DEFECTS. The ostium of the coronary sinus greatly enlarged. Defect between anterior wall of coronary sinus and left atrium.

CLINICAL MATERIAL

The patients have been operated on in the order of referring or of examination at the clinic when surgery appeared to be indicated. The age distribution is shown in Table 1, the sex distribution in Table 2 (19 men and 40 women). This corresponds to a normal distribution, cf. Swan's 32 male and 68 female patients.

TABLE 1. Age distribution at surgery.

Age in years	Number of patients
0–2	1
3–10	11
11–20	35
21–45	20
>46	2
Total	59

The reasons for presentation in the case of younger patients without complex defects have been the discovery of blowing systolic murmur or heart enlargement in routine examination. Older patients have generally come in on account of aggravated symptoms. In some

TABLE 2.

Type of defects	Method of operation: Circumclusion	Hypothermia	Extracorp. circulation	M	F	Total	Deaths
Septum secundum defects							
Central defect							
Simple	6	15	6 −1	8	19	27	1
Pulm. sten., acyan.			1 (1)[b] −1		1	1	1
cyan.	1		2 −1	2	1	3	1
Total anom. ven. return			2	2		2	
Mitral insufficiency			1		1	1	
Low (inf. caval) defect	(1)	(1)	6	2	4	6	
High (sin. ven.) defect	1	3	1	2	3	5	
Septum primum defects			1[c]	1		1	
Ostium atrioventriculare commune	(1)		11 −4	2	9	11	4
Coronary sinus defects			2		2	2	
Total	8 (2)	18 (1)	33 (1) −7	19	40	59	
Deaths	0	0	7				7

[a] Minus sign indicates deaths.
[b] Number within brackets indicates reoperation under extracorporeal circulation.
[c] Combined with hypothermia 30°C.

using this method despite the advent of extracorporeal circulation.

Murray (1948) suggested a suturing technique which was subsequently developed by Söndergaard (1954) and tested clinically by Björk & Crafoord (1953). It consisted of placing a suture in the septum around the defect. In 1954 Björk & Crafoord operated on 12 patients with a mortality of 2. Of Husfeldt's (1958) 70 patients, 40 % were repaired without demonstrable shunt.

In many cases the appearance of the intracardial defect is so complicated that it is impossible to form any definite opinion on its boundaries by palpation alone; a direct-vision attack has therefore been sought for. Developments in this direction are based on the studies of Haecker (1907) who showed that the heart tolerates inflow occlusion for a period of a few minutes. The time during which the circulation may be interrupted has been too short, however, for more complicated forms of intracardial operation. By their experimental attempts with hypothermia Bigelow, Callaghan & Hopps (1950) demonstrated the potentialities of hypothermia in intracardial surgery. By this means the circulation could be interrupted sufficiently long to permit an intracardial operation; Lewis & Taufic (1953) reported a successful direct-vision repair under hypothermia, and Blount, Swan, Gensini & McCord (1954) reported successful results on five patients as revealed by postoperative catheterization. At the same time as the number of patients operated upon under hypothermia has risen, the mortality has decreased; among, for example, Swan's (1958) last fifty-five patients there was not a single death, nor among Brom's last sixty-five patients with secundum defects.

Concomitantly with the rapid development of the use of hypothermia, the extracorporeal circulation technique has improved and been put to increasing use. Gibbon made the first successful intracardial operation under extracorporeal circulation in 1953. Lillehei (1955) used controlled cross-circulation for closure of, for example, ostium atrioventriculare commune. He has since adopted the de Wall bubble oxygenator, while the Mayo Clinic uses Gibbon's screen oxygenator (Swan, Wood, Burchell & Edwards 1955). Elsewhere, too, extracorporeal circulation is being increasingly used for closure of all varieties of atrial septal defect (Senning 1958).

ANATOMICAL CLASSIFICATION

The biology of the atrial septum has been described by Rokitansky (1875) and by Patten (1938). We have adopted the following classification.

1. INTERATRIAL SEPTUM SECUNDUM DEFECTS.

(*a*) *Central defects*. One or several defects of varying size, demarcated all round by atrial septal tissue.

(*b*) *Low defects*. The defects extend down to the inferior vena cava, the lower margin being apparently continuous with the caval valve. Often combined with anomalous pulmonary venous return and sometimes with patent foramen ovale.

(*c*) *High defects* (sinus venosus defects). The defect lies above the fossa ovalis

defects, leading to the operation of patients with secundum defect under extracorporeal circulation. In one case an ostium atrioventriculare commune was interpreted as a secundum defect; in attempts to place a circumclusion suture, an ostium atrioventriculare commune was discovered and the patient had to be reoperated under extracorporeal circulation. The value of angiocardiography for mapping of anomalous venous return can, however, not be overestimated.

INDICATIONS FOR SURGERY

We have followed the rule formulated at the Symposium on Atrial Septal Defects at the International Heart Congress in Stockholm in 1956 to operate all patients with a blood flow through the lesser circuit at least twice as great as through the greater circuit. In view of the low risk involved in operation under hypothermia, however, we are increasingly inclined to widen the indications to include all patients with atrial septal defects and a significant left-to-right shunt. We consider operation *contraindicated* only in patients whose pulmonary vascular resistance is so high that there is a predominant right-to-left shunt. During the period covered by this material only one patient (a 43-year-old woman) was refused for this reason.

Since most of the operations have been quite recent, we have been unable to perform postoperative catheterization except in a small number of patients. Our present purpose is to discuss the surgical technique and the primary results. Follow-up studies will be reported later.

As seen from Table 2, the material consists of 59 patients with defects at atrial level. Forty-five had secundum lesions, 27 of which were simple defects at the foramen ovale. Two of the latter were combined with total anomalous venous return. In 4 patients the defect was combined with pulmonary valvular stenosis, and in 1 with mitral insufficiency. Six patients had defects without lower limit towards the inferior vena cava, and five had high defects, so-called sinus venosus defects.

In one patient the defect was denoted as primum and was combined with mitral stenosis of congenital type. Eleven patients had ostium atrioventriculare commune and two coronary sinus defects.

OPERATIVE TECHNIQUES

Closed repair

We used the circumclusion method of Söndergaard and Björk & Crafoord. The pericardium is opened by subcostal incision under the fifth rib and the interatrial groove is dissected as suggested by Söndergaard. After palpation of the defect a ligature is inserted, in suitable cases, through the lower septal tissue either with a needle or, by Söndergaard's method, with a probe. The ligature is then tied round the defect in the dissected groove across a pericardial flap. With the finger in the atrium a check is made that the defect is closed on tightening of the ligature.

Septum secundum defects have been operated upon by circumclusion suture in ten patients. Six of them had persistent foramen ovale, one

cases the patient had had repeated incompensation attacks which demanded hospitalization and digitalis therapy over a period of several years. Patients with ostium atrioventriculare commune have presented at an earlier age owing to pronounced symptoms, usually accompanied by cyanosis on exertion.

PREOPERATIVE ASSESSMENT

In the *physical examination* the patients have usually had parasternal pulsations, all had typically systolic murmur in the left second to fourth intercostal spaces and accentuated second pulmonary sound. Complicated cases have had an additional pathological murmur such as the diastolic murmur with extension into the left axilla in cases of ostium atrioventriculare commune.

Roentgen has shown right heart enlargement, wide trunk and main branches of pulmonary artery, and increased amount of blood in pulmonary vessels.

Electrocardiogram. The possibility of distinguishing between a defect of secundum and of ostium primum type by means of the electrocardiogram has been demonstrated in recent years by Toscano-Barboza, Ely, Brandenburg & Burchell (1956). The ordinary electrocardiogram of a secundum defect shows right electrical axis deviation and partial right bundle branch block. In a very high percentage of primum defects left electrical axis deviation is found in combination with partial right bundle branch block. If a primum defect is combined with mitral insufficiency, there may also be signs of left-sided hypertrophy. The QRS vector rotates anticlockwise in the frontal plane. The electrocardiogram had this typical appearance in our cases of septum primum defect and A-V commune.

Physical working capacity. Of 28 patients examined by cycle-ergometry, 18 had normal or virtually undiminished and 10 diminished capacity.

Cardiac catheterization was performed in all cases in which the position, magnitude and direction of the shunt were determined. In two cases the shunt was calculated to be rather smaller than the flow in the systemic circuit, while in 21 cases the flow through the pulmonary circuit was two to three times, and in 25 cases more than three times, as great as in the systemic circuit. Patients with pulmonary stenosis and cyanosis, as also the ostium atrioventriculare commune cases, have also had a certain right-to-left shunt. In some cases the size of the atrial septal defect was estimated with a balloon catheter. Pressures have generally been normal in the right atrium, elevated in the ventricle, and there has often been a pressure gradient over the pulmonary ostium due to increase of blood flow.

Angiocardiography has previously been performed in all cases of atrial septal defects. It is now reserved for cases of suspected anomalous venous return or atrioventriculare commune. The lower edge of an atrial septal defect is difficult to visualize owing to the rotation of the heart. A lower septal margin and the presence of anomalous venous return have been distinctly demonstrated in 15 cases. In 21 cases, on the other hand, the findings were rather uncertain and there was some over-diagnosis of primum

patient became listless 30 hours after operation, and a few hours later developed epileptiform attacks and became unconscious. He was given curare and respirator treatment for two days Both these patients are completely restored. In the previously mentioned patient with low (inferior vena cava) defect, the inferior vena cava was first stitched to the left atrium by suturing the inferior caval valve to the defect. The patient was reoperated on the same day (Björk *et al.* 1959). She has since been reoperated under extracorporeal circulation. Two patients with secundum defects had auricular fibrillation and flutter prior to operation, and five patients flutter or fibrillation after operation. These arrhythmias were regularized with digitalis and quinidine. Otherwise there were no postoperative complications.

Open closure under extracorporeal circulation

Use was made of a Crafoord–Senning–AGA heart-lung machine[1] with right-sided thoracotomy through the fifth costal bed. The venous return is led off by gravity to the heart-lung machine and arterialized blood is returned through the femoral artery. The by-pass is adjusted to a blood flow of 2.7–2.2 litres per sq.m body area per minute; the time of perfusion varied between 11 and 91 minutes. After the by-pass has been started and the cavae occluded, the atrium is opened and at the same time the aorta is occluded, which causes cardioplegia due to anoxia. The reduced blood flow via the coronary arteries and the fact of the heart being practically stationary and flaccid facilitate the intracardial operation. Before the defect is completely closed, a cannula is inserted into the left atrium via the base of the right pulmonary veins in order to relieve the pulmonary circulation and to prevent distension of the left heart during the period immediately following the removal of the aortic clamp, when the contraction of the heart is weak. When the intracardial defect has been repaired and the incision in the right atrium nearly closed, the aortic clamp is released so that the coronary blood can fill the right heart, after which the incision is entirely closed. Concomitantly the cannula in the left atrium, which is connected to the suctioning device of the machine, is opened. When the heart is again contracting regularly and with good vigour, the cannula in the left atrium is closed and the heart-lung machine is stopped.

Nineteen patients with *septum secundum defects* were operated upon under extracorporeal circulation. Six with central defects were preoperatively suspected to be of primum type since no lower septal rim was demonstrable above the valvular plane by angiocardiography. These six defects were closed by simple suture. One of the patients died of cerebral embolism on the third day after operation. Autopsy revealed a thrombus in the left auricular appendage.

An acyanotic patient with the combination of foramen ovale and pulmonary stenosis developed severe tricuspid insufficiency after simple suture of the atrial septal defect and had to be reoperated under extracorporeal circulation on the same day, an Ivalon sponge prosthesis being sewn to the defect. Severe haemorrhage developed postoperatively, requiring thirty transfusions. The bleeding stopped after 24 hours. She was tracheotomized but died suddenly with a picture of central circulatory collapse on the fifth day after operation.

One of the two cyanotic patients with atrial septal defect and pulmonary stenosis could not maintain satisfactory systemic circulation after valvulotomy and closure of the defect, and died after 12 hours. Autopsy revealed an enormously underdeveloped right ventricle. The other cyanotic patient had no postoperative complication.

[1] Manufactured by AGA, Lidingö, Sweden.

was cyanotic owing to combination with pulmonary stenosis. One had a sinus venosus defect, one a low (inferior caval) defect, and the tenth had an ostium atrioventriculare commune.

The six cases of simple foramen ovale were repaired by typical circumclusion suture. The patient with pulmonary stenosis and cyanosis still has a right-to-left shunt and signs of pulmonary stenosis after operation of the defect and valvulotomy. This patient has not been recatheterized, but a ventricular septal defect appears to be present. The patient with high (sinus venosus) defect and anomalous venous return was repaired by circumclusion and transplantation of the vein of the upper lobe to the vein of the middle and lower lobes.

Two additional patients had a preoperative diagnosis of septum secundum defect. An ostium atrioventriculare commune was found in one at operation. A ligature was applied, but the attempt to tighten it produced total atrioventricular block. This disappeared when the ligature was loosened. The poor postoperative condition of the patient compelled reoperation on a vital indication on the following day with extracorporeal circulation. This patient died on the second postoperative day. The second patient could not be repaired on account of a low (inferior caval) defect and anomalous venous return, but was successfully reoperated later with extracorporeal circulation.

In the eight cases in which circumclusion could be applied the postoperative course was uneventful. Two patients have been recatheterized and no shunt was discovered. Roentgen showed a diminution of heart size.

Open repair under hypothermia

Surface cooling, as used by us, was done on an operating table specially designed by Adams-Ray, Persson & Heljestrand. The patient is placed from the outset in the position suited for operation and is cooled to 30°C with cold air. Cooling takes place partly during the surgery and rewarming is started immediately after occlusion. The patient is lightly hyperventilated, and pH, PCO_2 and standard bicarbonate (Aastrup) are checked at frequent intervals. No drugs are administered. In the majority of cases right-sided thoracotomy has been done with incision at the lower border of the fifth rib from the sternal edge to the posterior axillary line with the right side tilted upwards about 60°. The venae cavae are dissected intrapericardially and the sling ligature round the inferior vena cava is placed as far as possible from the atrium. At the same time the right pulmonary veins are dissected so that a clamp can be applied to them. When the temperature has fallen to the desired value, the venae cavae are occluded, the respirator is disconnected, a clamp is applied to the right pulmonary veins to prevent emptying of blood and filling with air while the atrium is open. When the blood pressure has fallen to 60 mm Hg, the aorta is occluded. The right atrium is incised and emptied of blood. The defect is closed with two rows of over-and-over sutures (00 silk). The clamp on the pulmonary veins is removed, the lungs are inflated so that the left atrium becomes overfilled with blood and air is driven out. The sling ligatures on the venae cavae are released, thus filling the right auricle. The incision is sutured. A maximum of 7 minutes' occlusion has been used.

Nineteen patients were operated upon under hypothermia. One of them was operated upon twice on the same day and later reoperated with the aid of a heart-lung machine. The operations of the 15 central defects and the 3 high secundum defects (sinus venosus) proceeded without complication. One patient had a suspect aphasia and possibly mild paresis of the facial nerve for two days postoperatively. Another

[1] Auto-Hypotherm, manufactured by A.B. HELJESTRAND, Stockholm.

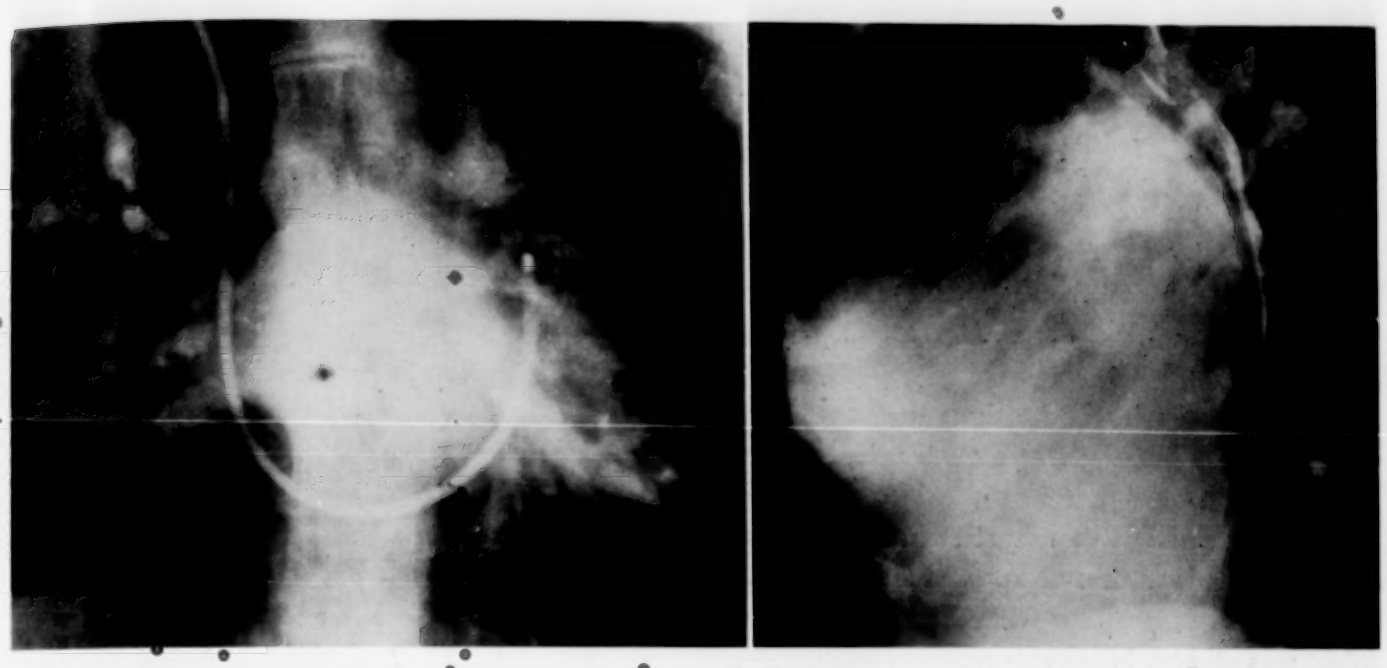


FIG. 3. Postoperative angiocardiography after correction of total anomalous venous return. (Courtesy of B. Nordenström.)

Two cases exhibited the combination *foramen ovale* and *total anomalous venous return*. In one of them the pulmonary veins behind the left atrium were fused into a common trunk which emptied into the superior vena cava (Fig. 1). In the other the common trunk emptied into the superior vena cava and the upper part of the right atrium. By right-sided thoracotomy, as in closed operative technique (Senning, 1958), a wide incision was made in the left atrium and the atrial septal defect was sutured from the left atrium, after which anastomosis was established between the common trunk, into which the pulmonary veins opened, and the incision (Fig. 2). The anomalous communication with the superior vena cava was divided. The first case ran an uncomplicated course, and recatheterization and angiocardiography showed entirely normal anatomy and normal haemodynamics (Fig. 3). The second case had pulmonary hypertension and highly increased vascular resistance in the pulmonary circuit. He was successfully operated on according to the same principles. He needed a period of postoperative respirator treatment; a follow-up examination has not yet been made.

A 39-year-old woman with a large foramen ovale defect had pronounced mitral insufficiency, probably on an endocarditic basis (Fig. 4). She was a severe invalid and had been repeatedly hospitalized for incompensation. A mitral annuloplastic operation was performed and an Ivalon sponge prosthesis was sutured to the defect. As frequently before the operation, she had auricular fibrillation postoperatively but no other complication.

Six patients had low septal defects (inferior vena cava), three of them with, in addition, persistent foramen ovale. Two of the latter had anomalous venous return. Patients with anomalous venous return were repaired by cutting the septum to form an anterior flap and transplanting it to the right of the pulmonary veins.

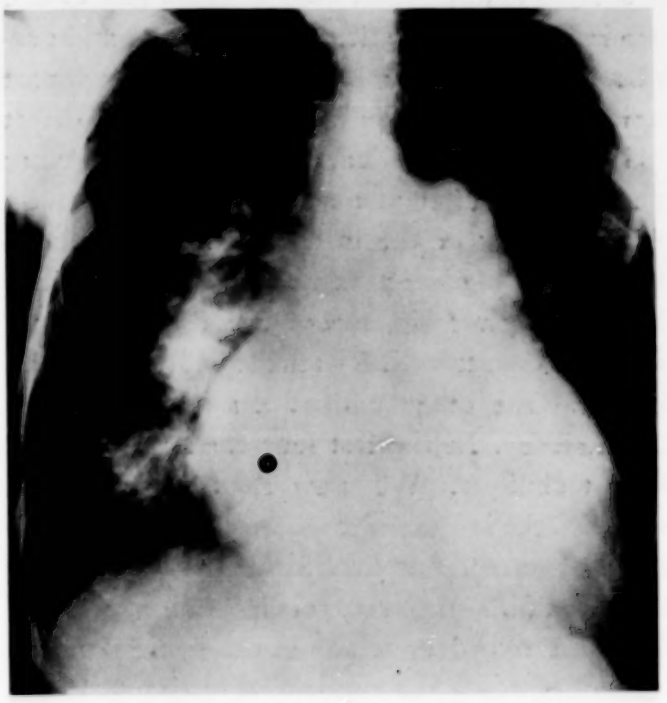
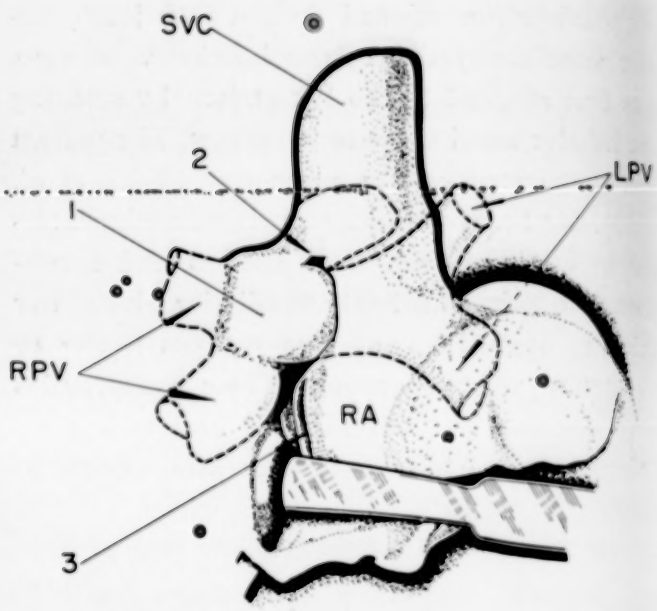


FIG. 4. Preoperative roentgen of heart with mitral insufficiency and atrial septal defect.



a



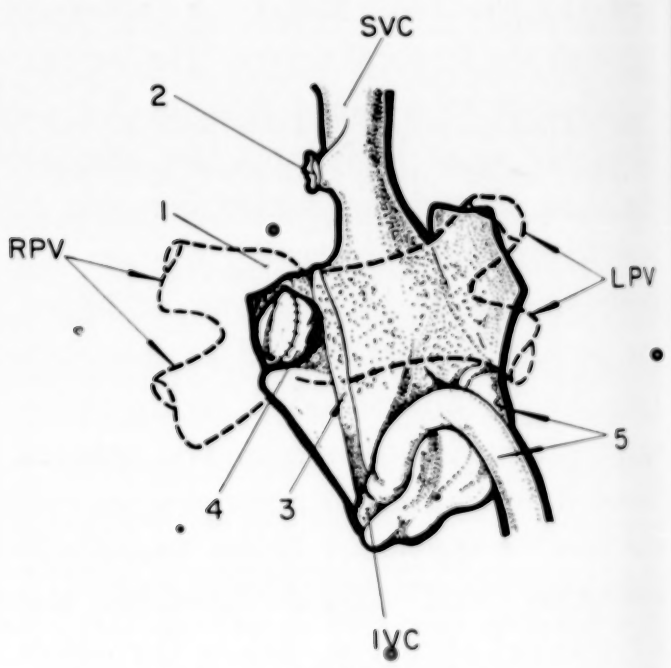
b

FIG. 1, *a* and *b*. Total anomalous venous return. Pericardium opened wide by right-sided thoracotomy.

SVC, superior vena cava; *RPV+LPV*, right and left pulmonary veins with common trunk; *RA*, right atrium; *1*, common pulmonary venous trunk; *2*, communication between pulmonary vein trunk and superior vena cava; *3*, pericardial reflection line attached to posterior margin between right and left atria.



a



b

FIG. 2, *a* and *b*. Total anomalous venous return. Anastomosis established between left atrium and common pulmonary venous trunk.

SVC, superior vena cava; *RPV+LPV*, right and left pulmonary veins with common trunk; *RA*, right atrium; *IVC*, inferior vena cava; *1*, common pulmonary venous trunk; *2*, communication between pulmonary venous trunk and superior vena cava is now tied; *3*, pericardial reflection line attached to posterior margin between left and right atria.

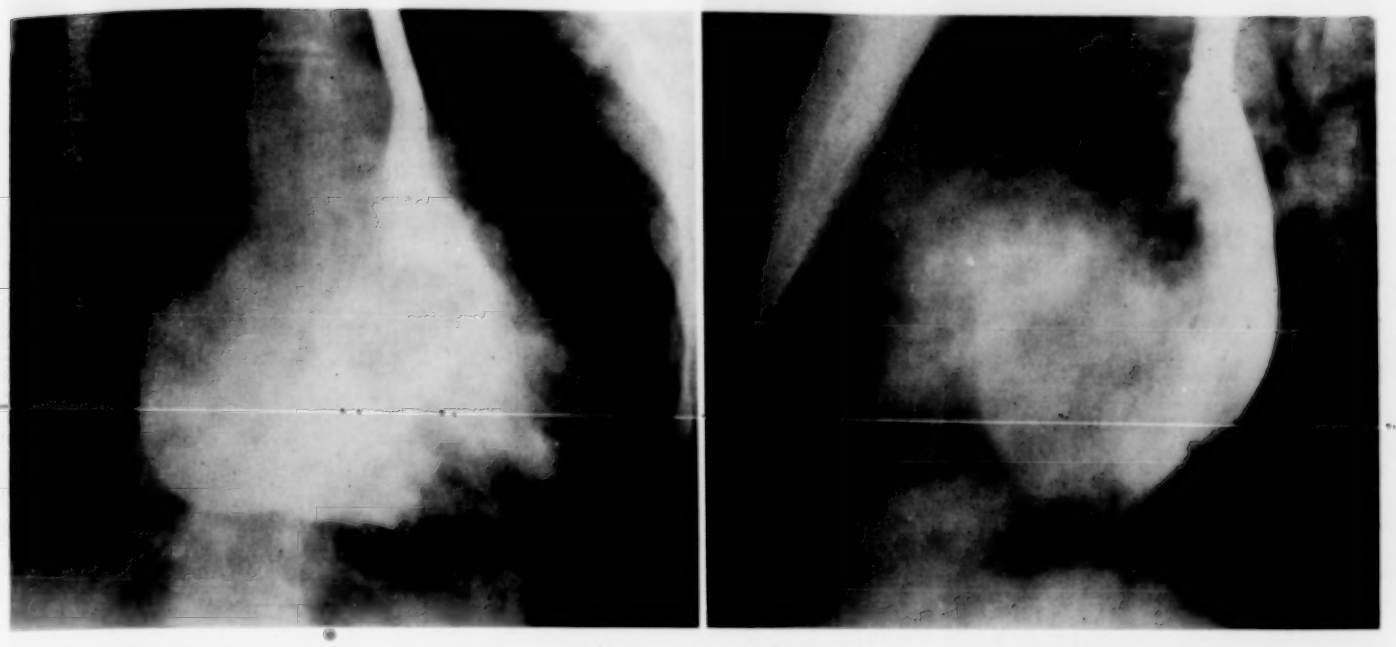


FIG. 6. Coronary sinus defect. Angiography; injection in a persistent left superior vena cava shows a widened coronary sinus with contrast defect caused by a left to right shunt. (Courtesy of U. Rudhe.)

cava, after which the septal defect was closed. In the other case the defect was closed by a prosthesis stitched at the lower end to the left of a large coronary vein emerging close to the opening of the coronary sinus. The first case has been re-examined by catheterization and angiocardiography and shows normal conditions, as does the second case re-examined by catheterization.

POSTOPERATIVE MANAGEMENT

The patient is carefully watched postoperatively in respect to temperature, blood pressure, pulse and breathing. Liquids are restricted, loss from drainage is replaced with blood, and tracheotomy and respirator treatment are introduced on the least sign of respiratory insufficiency. All patients receive penicillin and usually streptomycin.

DISCUSSION

From the practical surgical aspect it appears difficult to classify atrial septal defects on the basis of supposed disturbances of embryological development, but we consider it better to distinguish the defects according to anatomical localization and type. We have included ostium atrioventriculare commune among defects at atrial level although such defects are related to the upper part of the membranous ventricular septum, sometimes descending into the muscular ventricular septum.

We have classified one case as a primum defect, in which there was no septal tissue above a part of the valvular plane. The defect was combined with mitral stenosis of congenital type. The stenosis was possibly a disturbance of development analogous to splitting of the valves in ostium atrioventriculare commune.

The series contains two cases of total anomalous venous return combined with foramen ovale. The malformation is partially of entirely different embryological origin, but was included owing to its surgical interest.

The technique employed in the first

Of the other four, two were reoperations after previous operation under hypothermia. One of each was repaired with a prosthesis and one by simple suture. Three of the six patients with low defect were tracheotomized. The remainder ran an uneventful postoperative course. Two recatheterized patients exhibited normal conditions and the remainder were observed clinically to be repaired.

One patient with high (sinus venosus) defect was sutured direct without complication.

One patient had a defect classified as *primum*. It was combined with mitral stenosis. Anterior and posterior commissurotomy was first performed in the mitral valve, after which the atrial septal defect was closed. No postoperative complication developed.

Ostium atrioventriculare commune was present in 11 cases. A cleft mitral valve alone was sutured in 3 patients, after which the defect was repaired with a prosthesis in two and by simple suture in one case. Of these 11 patients one was reoperated on the following day after an attempt at repair by circumclusion suture. The patient was in extremely poor condition and died two days after the operation. Another patient died of atrioventricular block. In a fourth patient the attempt was made to widen an extremely narrow mitral ostium by stitching a prosthesis to the cleft mitral valve. The patient was primarily well but suffered a sudden deterioration after 3 weeks and died 6 weeks after the operation. In three cases an hourglass-shaped prosthesis was applied, one part being stitched to the ventricular septal defect below the atrioventricular valves and the other part to the defect at atrial level simultaneously with suturing of the cleft mitral and tricuspid valves. One of these patients had a residual mitral insufficiency and died three weeks after operation. She had been treated for anuria with an artificial kidney. One other patient has signs of mitral insufficiency. In the last four cases we changed our technique. We now start by repairing the defect in annulus fibrosus in order to restore normal function at the valvular plane and diminish the risk of insufficiency (Fig. 5). Cleft mitral or tricuspid valves are repaired by suture along the surfaces of contact. When annuloplastic surgery was performed, the defect at atrial level was so small in two cases that a simple suture was employed, while two other cases required prostheses. Two patients had transient total atrioventricular block and one received respirator treatment. These patients are in good condition without definite sign of mitral insufficiency.

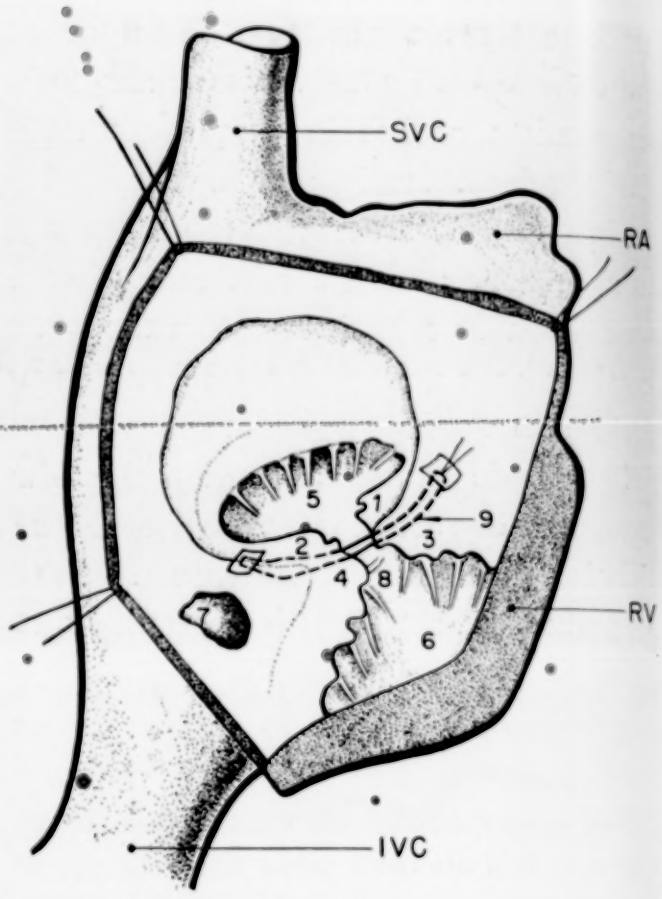


FIG. 5. Annuloplasty performed by a double suture (*9*) from the anterior annulus fibrosus tissue close under the valve, through the gap between the valves, close under the posterior valve into the posterior annulus fibrosus tissue, and back the same way. Each end of the suture is reinforced with an Ivalon sponge prosthesis and tightened until the valves appear to be competent.

SVC, superior vena cava; *IVC*, inferior vena cava; *RA*, right atrial appendage; *RV*, opened right ventricle; *1–2*, cleft mitral valve; *3–4*, cleft septal cusp of tricuspid valve; *5*, mitral orifice; *6*, tricuspid orifice; *7*, coronary sinus; *8*, ventricular septum; *9*, annuloplastic suture.

Two patients have had left-to-right shunt owing to *coronary sinus defect*. In one there was a wide coronary sinus into which a left vena cava emptied. It was wide open to the left atrium owing to a defect in the anterior wall (Fig. 6). The atrial septum was cut and the vena magna cordis stitched end-to-end to a persistent left superior vena

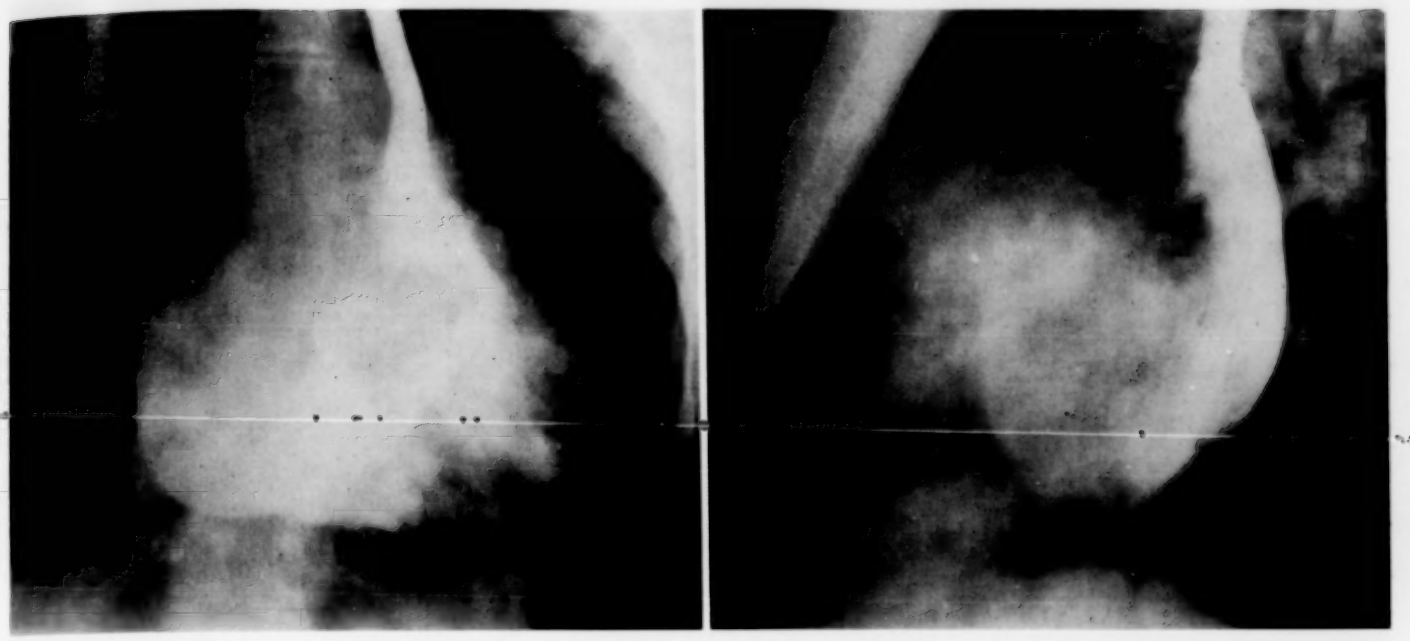


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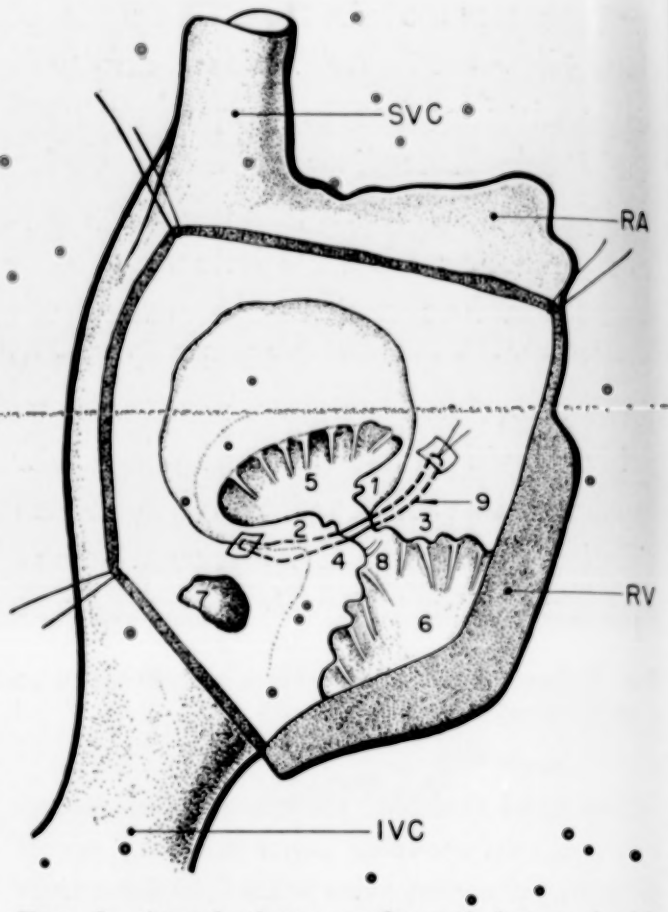


FIG. 5. Annuloplasty performed by a double suture (*9*) from the anterior annulus fibrosus tissue close under the valve, through the gap between the valves, close under the posterior valve into the posterior annulus fibrosus tissue, and back the same way. Each end of the suture is reinforced with an Ivalon sponge prosthesis and tightened until the valves appear to be competent.

SVC, superior vena cava; *IVC*, inferior vena cava; *RA*, right atrial appendage; *RV*, opened right ventricle; *1–2*, cleft mitral valve; *3–4*, cleft septal cusp of tricuspid valve; *5*, mitral orifice; *6*, tricuspid orifice; *7*, coronary sinus; *8*, ventricular septum; *9*, annuloplastic suture.

Two patients have had left-to-right shunt owing to *coronary sinus defect*. In one there was a wide coronary sinus into which a left vena cava emptied. It was wide open to the left atrium owing to a defect in the anterior wall (Fig. 6). The atrial septum was cut and the vena magna cordis stitched end-to-end to a persistent left superior vena

septal defect can be closed from the incision in the left atrium.

Several of the patients were tracheotomized and given respirator treatment postoperatively since, even in mild ventilatory insufficiency, we prefer to assist the patient's respiration artificially. In our opinion respirator treatment has great advantages, especially for patients with pulmonary hypertension.

Open cardiotomy is now preferred to closed repair for correction of defects at atrial level. Extracorporeal circulation with a heart-lung machine provides the best means of closing even complicated defects, but is still so expensive and requires so much blood that hypothermia is preferred when feasible.

We imagine that in future we shall generally use hypothermia, as now, for defects at atrial level. When unexpected technical problems are encountered, a disposable simple heart-lung machine can be connected, which allows a sufficiently long operating time.

SUMMARY

An account is given of 59 cases of atrial septal defects operated upon by closed repair and by open surgery under hypothermia and with extracorporeal circulation. Techniques and primary results are discussed. The mortality was 4 out of 11 patients with ostium atrioventriculare commune and 3 out of the remaining 48 patients.

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part of the series was closure with circumclusion suture. This procedure has its limitations. It is difficult to close inferior cava defects, and some cases of partial anomalous venous return and ostium atrioventriculare commune cannot be operated upon. Since in other series as well (Husfeldt, 1958) there has been a high percentage of residual shunts, we now prefer an open technique and the simpler defects are preferably repaired under hypothermia. Surface cooling is employed and no drugs are administered to influence heart rhythm during occlusion. Our experience is too limited, however, to judge whether this may affect the frequency of ventricular fibrillation. When using solely right-sided thoracotomy we have seen air rise into the right pulmonary veins, and we now consider it important to have a clamp on these veins during the period in which the atrial septal defect is open in order to avoid air embolization.

More complicated defects are operated upon under extracorporeal circulation in view of the advantage of the prolonged operating time. With extracorporeal circulation it is chiefly ostium atrioventriculare commune which involves technical problems. Some of these defects are of such severity as to be inoperable at the present time. We consider it essential at present to perform annuloplastics so as to obtain support for the valvular mechanism during systole, thus diminishing the risk of insufficiency. Annuloplastic surgery also reduces defects in ventricular and atrial septa and often permits their closure by simple suture. A practical detail is that the mitral and tricuspid valves should, if possible, be so sutured that their contact surfaces abut one another.

In the repair of ostium atrioventriculare commune atrioventricular block is a great danger. We attempt to place sutures parallel with the upper edge of the ventricular septum and not transversally. Of three patients who developed atrioventricular block one died, while two had transitory block which lasted between a few hours and four days. We now consider it generally advisable to place pacemaker electrodes in all these patients for use in the event of total atrioventricular block.

With a combination of atrial septal defect plus pulmonary valvular stenosis plus cyanosis it is, of course, essential to start with valvulotomy. If the right-to-left shunt then disappears at the atrial level, the defect can be closed. If the right-to-left shunt persists, we consider, like Brom, that the defect should not be closed until the shunt has reversed.

The correction of coronary sinus defects may constitute a problem. If they are closed direct, most of the venous blood of the heart enters the left side In one case, therefore, we preferred to let the coronary sinus empty into a persistent left vena cava; in another the greater portion of the venous blood was redirected to the right side by means of a prosthesis. Two small veins still empty into the right side, but recatheterization has not revealed any lowering in oxygen saturation of the arterial blood.

If total anomalous venous return is operated from the right side, the dorsal side of the heart is most accessible; from this approach there is no need even to open the right atrium, but the atrial

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Surgically Corrected Case of Transposition of the Great Vessels

BENGT JONSSON, CARL-OLOF OVENFORS and ÅKE SENNING

Several methods have been suggested for surgical correction of complete transposition of the aorta and pulmonary artery, some of them by operation on the arterial level (Bailey, Cookson, Downing & Neptune, 1954; Björk & Bouckaert, 1954; Blombäck, Blombäck, Senning & Wallén, 1955; Kay & Gross, 1955; Mustard, Chute, Keith, Sirek, Rowe & Vlad, 1954; Senning, 1958). Considerable improvement has been brought about in a number of surviving patients by operation on the venous level (Blalock & Hanlon, 1950; Graanboom, 1953; Lillehei & Varco, 1953), particularly with Baffes' method (Baffes, 1956). Merendino, Jesseph, Herron, Thomas & Vetto (1957) have tried interatrial venous transposition with the help of a plastic prosthesis, and Albert (1955) tested experimentally the use of an anterior flap of the atrial septum for correction.

A new method for surgical correction of transposition of the great vessels has recently been described by one of us (Senning, 1958). An account is given in the present paper of the clinical, physiological and roentgenologic findings in a patient operated on with this method.

The techniques used in cardiac catheterization and angiocardiography were the same as those described in earlier reports from our hospital (Kjellberg, Mannheimer, Rudhe & Jonsson, 1955).

CASE REPORT[1]

A. S., a boy, b. 9/1 1948. He had been cyanotic since birth. At 18 months, he had a convulsive attack with fever. He had never been a squatter. On his first admission to hospital in February 1954, he was able to walk about 100 metres on the level. Physical examination showed deep cyanosis and marked clubbing of the fingers and toes. There was no precordial bulge and no systolic thrill. A marked parasternal lift was present. The second heart sound was accentuated and pure. A short, early-systolic, grade II murmur was heard over the second

[1] The preoperative studies, made at the pediatric clinic, Karolinska sjukhuset, have earlier been reported by Kjellberg, Mannheimer, Rudhe and Jonsson.

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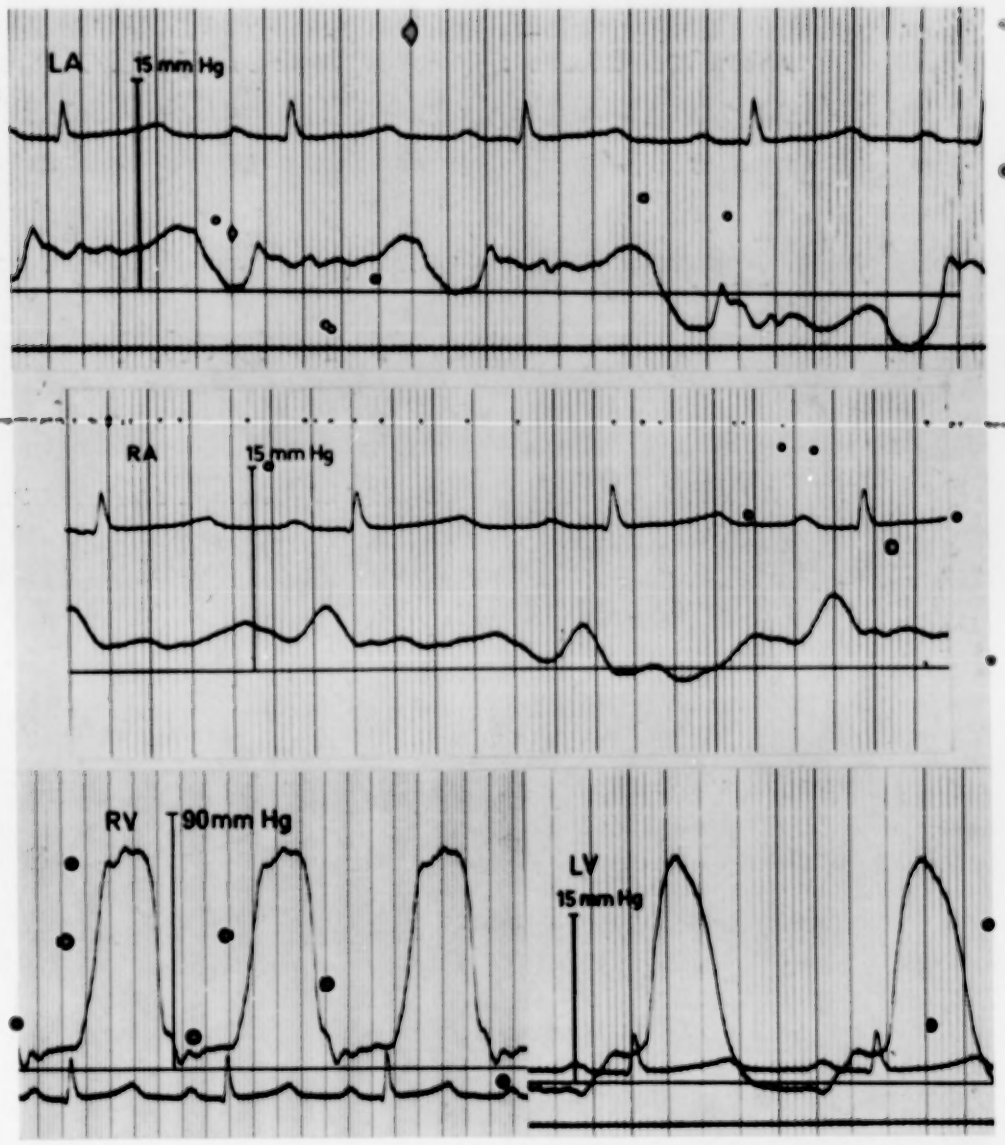


FIG. 2. Preoperative pressure recording from left atrium (LA), right atrium (RA), right ventricle (RV) and left ventricle (LV). In the right ventricle, the systolic pressure is on the same level as normal pressure in the systemic circuit, and that in the left ventricle as in the pulmonary circuit. The left atrium shows greater respiratory variations in pressure than the right. The shape of the curve for the left atrium is abnormal, with a rapid fall in pressure after the peak of the *v* wave. This can be explained by the left ventricle being abnormally thin-walled, and therefore presenting less resistance during the rapid filling phase.

a mutual variation in the atrial pressures during respiration, thus allowing the possibility of an interatrial shunt in alternating directions. During inspiration, the left atrial pressure was lower than the right, and during expiration *vice versa*. The systolic pressure in the right ventricle was high (78 mm Hg), whereas that in the left ventricle was low (19 mm Hg). Contrary to the normal conditions, the hypertrophied right ventricle presented greater resistance to diastolic filling than did the left ventricle. During ventricular diastole, an unusually rapid fall in pressure was observed in the left atrium, on opening of the mitral valve (Fig. 2). Since the pressure in the right atrium was higher than in the left during ventricular diastole, a right to left interatrial shunt could take place. During ventricular systole, on the other hand, the pressure was higher in the left atrium and the prerequisites therefore existed for a left to right shunt.

Selective angiocardiography was perfor-

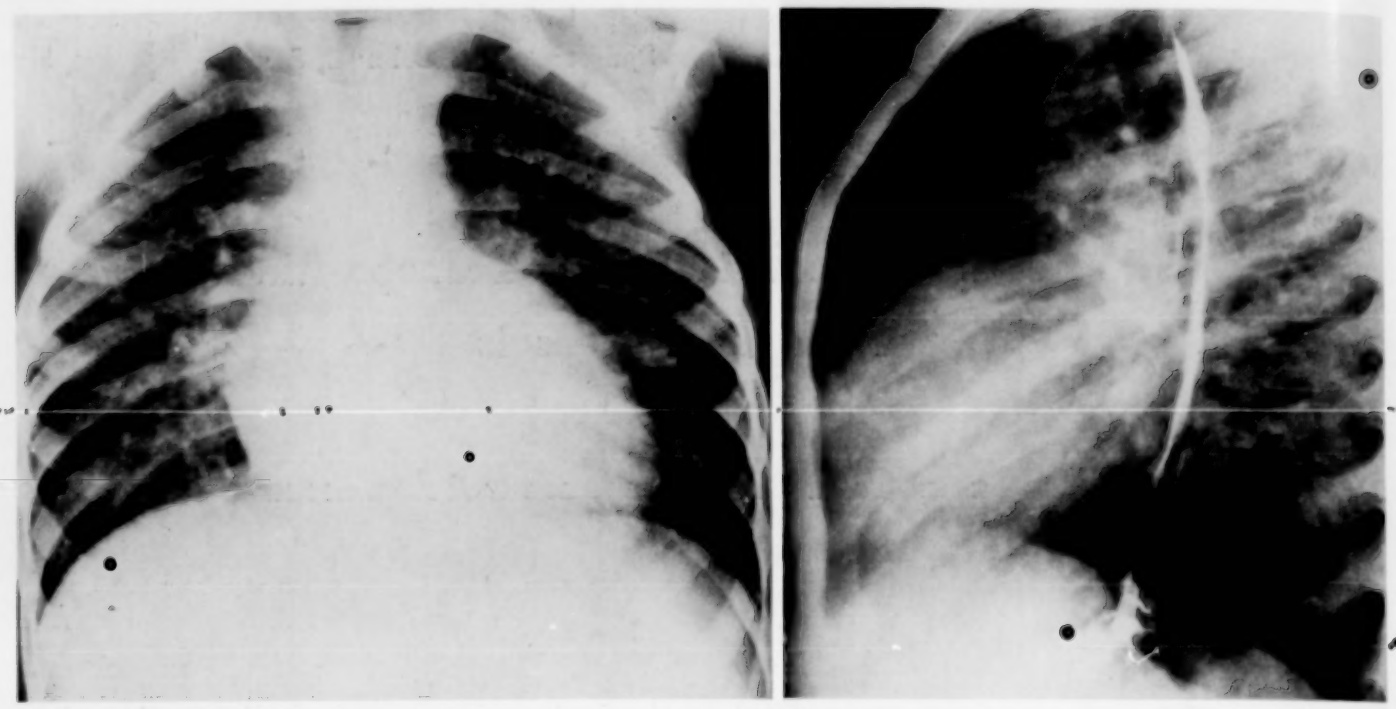


FIG. 1. Preoperative roentgenologic examination. Moderate enlargement of heart. Considerable dilatation and hypertrophy of right ventricle. No signs of atrial enlargement. The vascular pedicle is not narrower than normal, but the main trunk of the pulmonary artery cannot be identified. Greatly increased vascularity of lungs.

L.I.S. The ECG showed signs of pronounced right ventricular hypertrophy.

On plain roentgenograms (Fig. 1), the pulmonary vessels were fairly markedly dilated, as a sign of increased blood flow. No typical narrow vascular pedicle was observed, but the main trunk of the pulmonary artery could not be identified at the normal site. No indications of atrial enlargement were present.

Cardiac catheterization was performed on March 3; the results are shown in Table 1. The catheter could be advanced into all the chambers of the heart, into the left side through an atrial septal defect. It was not, however, possible to enter the pulmonary artery and aorta. A mixed shunt was present at the atrial level, and repeated sampling of the blood showed that the shunt varied from one moment to the next.

Analysis of the pressure curves showed

TABLE 1. Findings on cardiac catheterization.

	Before operation 9.3.54	After operation 7.7.58
Age, yrs.	$6^{2}/_{12}$	$10^{6}/_{12}$
Length, cm	108	126
Weight, kg	14.6	22.0
O_2 saturation, %		
SVC	56	70
IVC	60	70
RA	68	—
LA	82	65
PV	97	—
RV	68	—
LV	86	67
PA	—	66
Syst. art.	69	93
O_2 cap., vol. %	28.4	28.8
Pressure, mm Hg		
SVC	—	7
IVC	—	6
RA	3	—
LA	2	6
RV	78/8	—
LV	19/3	15/2
PA	—	14/6
Aorta	86/63	—

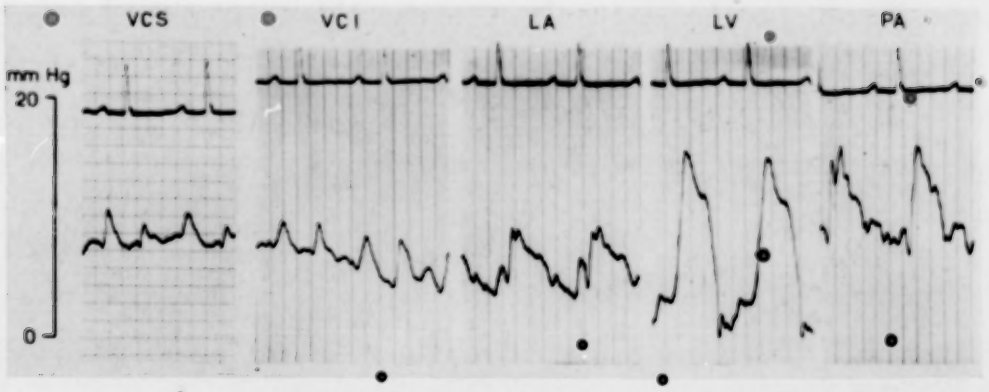


FIG. 4. Pressure recording at postoperative catheterization, from superior vena cava (VCS), inferior vena cava (VCI), the venous part of the anatomic left atrium (LA), left ventricle (LV) and pulmonary artery (PA).

ing aorta took place through a wide backward arch in the sagittal plane. No demonstrable ventricular septal defect or patent ductus arteriosus was present. The left ventricle was somewhat thin-walled, smaller than the right ventricle, and lay behind it. The main trunk of the pulmonary artery was given off from the left ventricle; it was unusually short, and lay in the midline behind the aorta.

Preoperative diagnosis: complete transposition of the great vessels and atrial septal defect.

Operation (transatrial correction of transposition with Senning's method) was performed on June 10, 1958. Though a trans-sternal thoracotomy, the right atrium was incised parallel to the vena cava and in front of it. An atrial septal defect about 17 mm in diameter was present at the site of the foramen ovale; the lower part of the septum was thin, and had small perforations. This part was excised, after which a posterior flap was made of the rest of the septum. This flap was sutured to the posterior wall of the left atrium and in front of the pulmonary veins. The posterior part of the right atrial wall was sewn into the atrial septal defect and to the right of the coronary sinus, as well as in front of both caval veins, so that these opened into the anterior part of the left atrium, through the atrial septal defect created. The right pulmonary veins were incised parallel to the posterior margin of the right atrium. The lateral margin of the incision was then sutured to the anterior margin of the incision in the right atrium. In this way, an arterial atrium was created, consisting of the posterior part of the left atrium, and the anterior part of the right atrium.

Operation was performed under extracorporeal circulation with the Crafoord–Senning–AGA heart-lung machine. During operation, the arterial oxygen saturation was 40 % before correction, and 93 % after correction. Prophylactic tracheotomy was performed.

The patient was kept in a respirator for three days. The postoperative course was, on the whole, uneventful. The ECG was recorded daily. Sinus rhythm was present, with normal P-Q time; the appearance of the P waves was unchanged.

Postoperative cardiac catheterization and

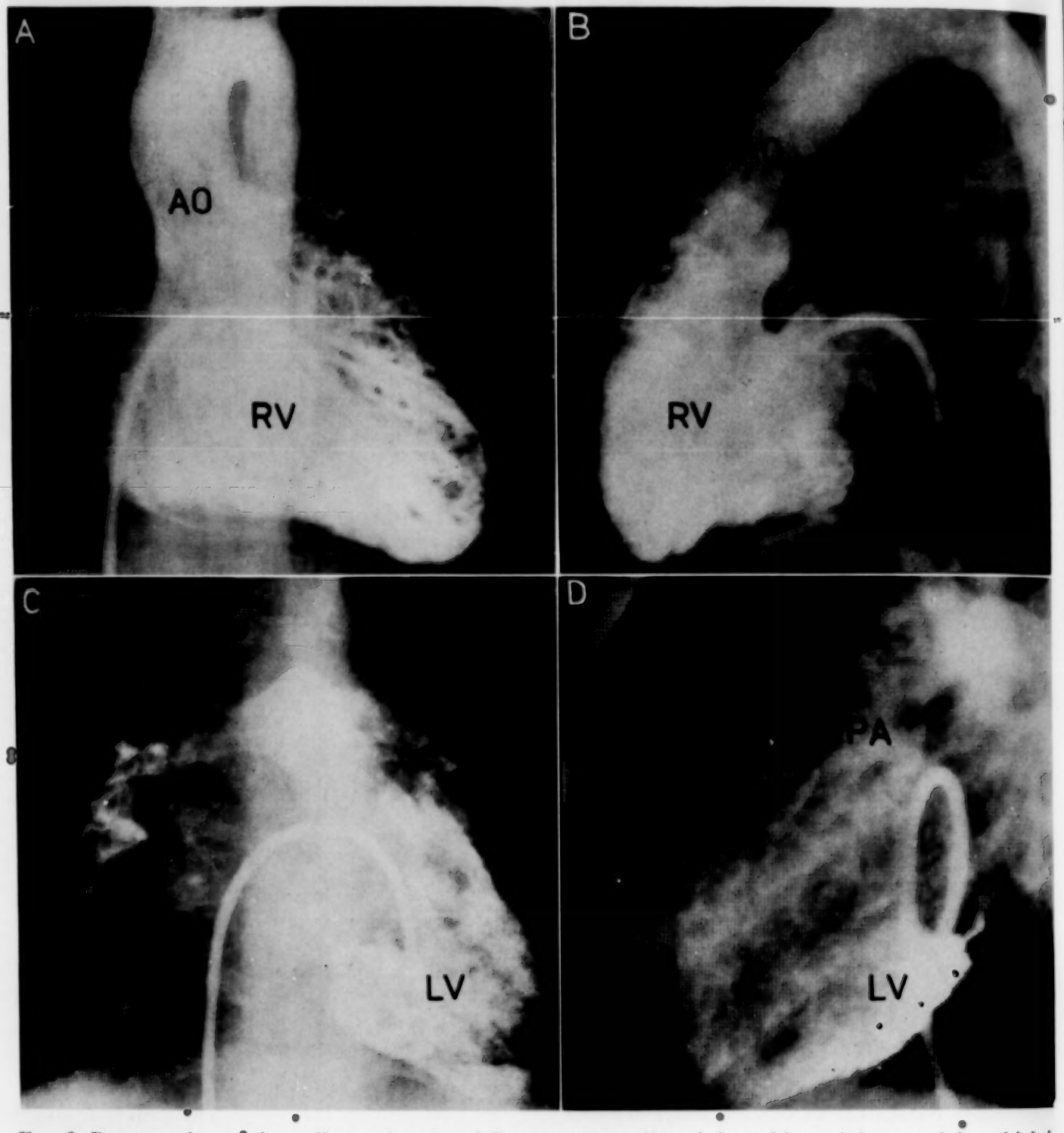


FIG. 3. Preoperative angiocardiography. *A* and *B*, contrast medium injected into right ventricle, which is thick-walled and dilated. A wide aorta is given off from it; the vessel runs in a backward arch close to the sagittal plane. No ventricular septal defect or patent ductus arteriosus are visible. *C* and *D*, contrast medium injected into left ventricle, via a catheter which advanced through an atrial septal defect. The main trunk of the pulmonary artery lies behind the aorta, and is shorter than normal. Left ventricle smaller than right, and fairly thin-walled. AO, aorta; LV, left ventricle; PA, pulmonary artery; RV, right ventricle.

med twice, with injection of contrast medium into the right and left ventricle, respectively (Fig. 3). The anteriorly situated right ventricle, with a typical crista supraventricularis, was fairly markedly dilated and hypertrophic. Its infundibulum was displaced upwards and to the right. The moderately dilated ascending aorta was given off ventrally from it; the transition into the descend-

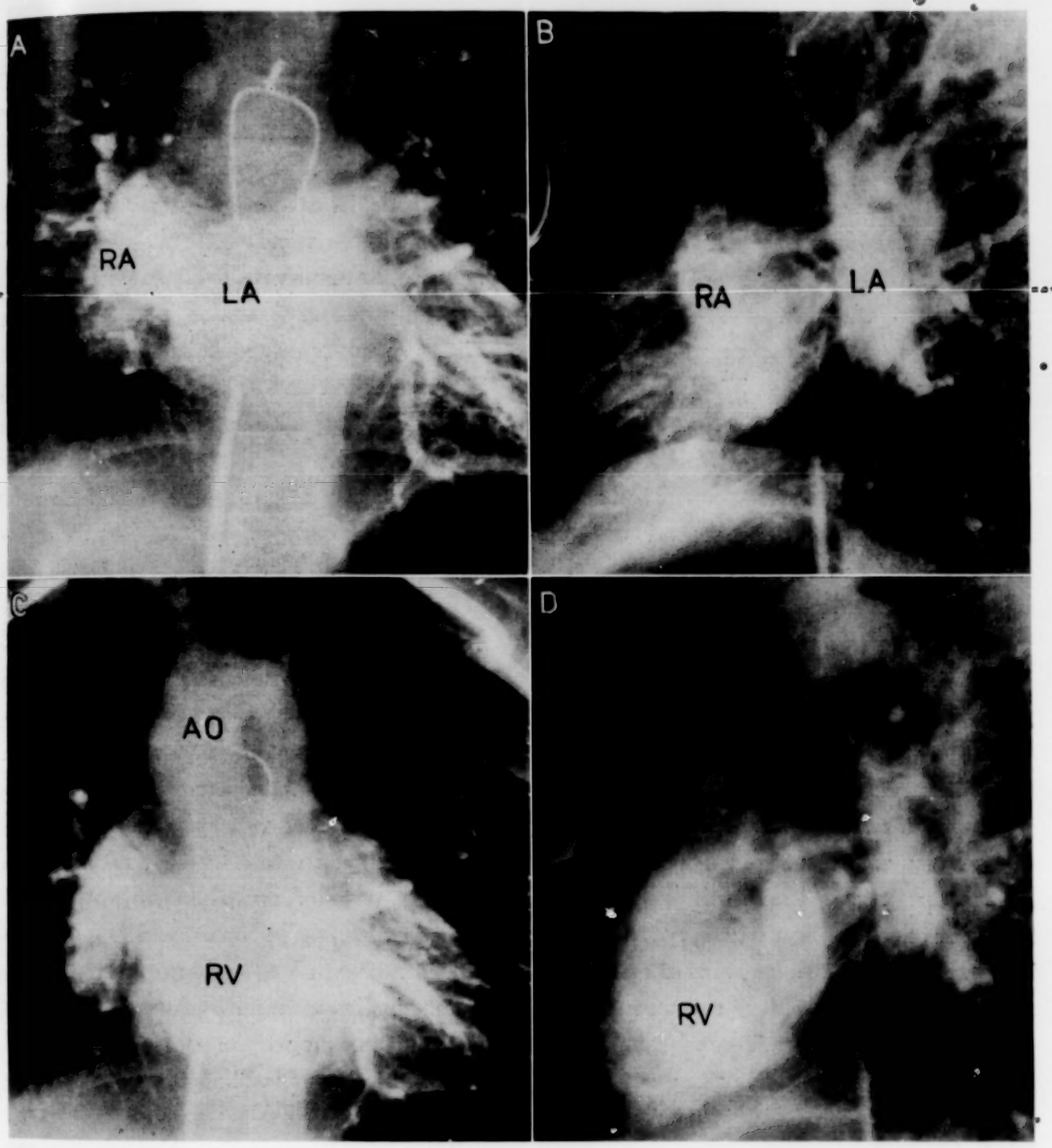


FIG. 6. Postoperative angiocardiography. Arterial phase, *A* and *B*. The pulmonary veins open into the new arterial atrium. This consists of the posterior part of the left atrium and anterior part of right atrium. No hindrance to passage between the two chambers of the arterial atrium, which has a large volume compared to that of the venous atrium. *C* and *D*, good passage through the tricuspid valve to the right ventricle, which is smaller than before operation, but still shows signs of hypertrophy. AO, aorta; LA, posterior part of left atrium; RA, anterior part of right atrium; RV, right ventricle.

orifice into the left ventricle, and thence into the pulmonary artery.

No pressure gradient was present between the inferior vena cava, superior vena cava and the venous atrium (Fig. 4). No intracardiac shunts were demonstrable. The pressure in the pulmonary artery was normal, and the systolic pressure in the left ventricle was low, as before operation, and cor-

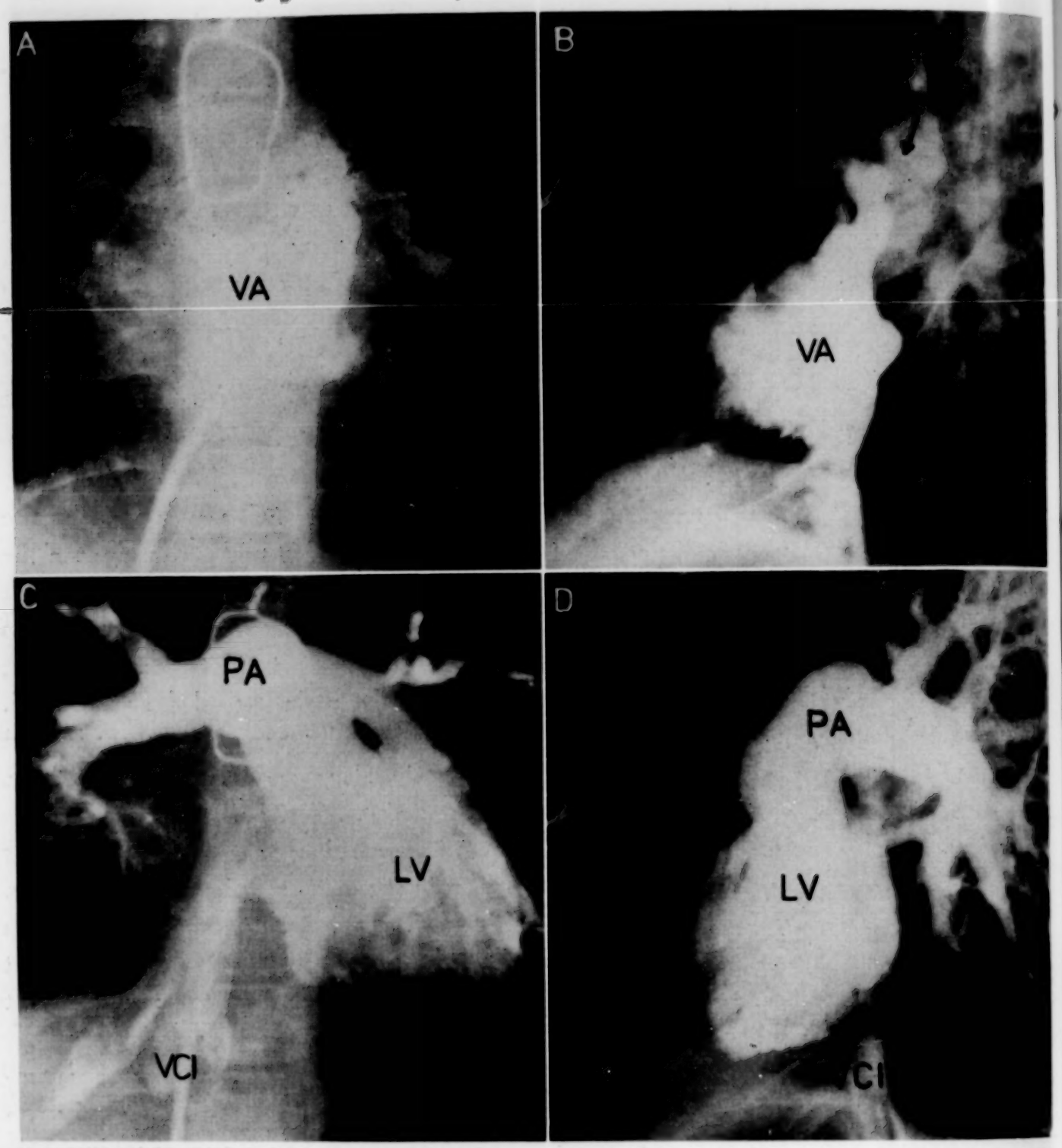


FIG. 5. Postoperative angiocardiography. Venous phase. Contrast medium injected into the newly created venous atrium; reflux to caval veins. *A* and *B*, the venous atrium now consists of the posterior part of the right atrium and anterior part of left atrium. The new atrium is fairly small, and its shape is irregular. No stenosis at opening of caval veins. Arrow points to left atrial appendage. *C* and *D*, $\frac{1}{2}$ sec. later. No impediment to filling of left ventricle and pulmonary artery. Left ventricle of same size as before operation. Pulmonary artery wider than normal. LV, left ventricle; PA, pulmonary artery; VA, venous atrium; VCI, inferior vena cava.

angiocardiography were performed on July 7 (Table). The whole examination was carried out under general anaesthesia. The somewhat low arterial oxygen saturation can be explained by decreased ventilation during Avertin anaesthesia. The catheter passed from the inferior vena cava, via the new venous atrium, into the superior vena cava. It was also possible to advance through the mitral

mitral leaflets towards the atrium during isometric contraction may imply a relatively appreciable narrowing of the space.

The arterial atrium, which has a considerably larger volume than the venous atrium, also consists of two communicating chambers, without signs of stenosis (Fig. 6, A–B). Its emptying ability also seems to be good (Fig. 6, C–D). The low pressure in the pulmonary artery is a further indication of the efficient function of the arterial atrium. Thus, operation seems to have produced good results from the haemodynamic point of view.

Patients with intact ventricular septum and a mixed shunt at the atrial level are the ideal cases for this type of operation. This is because pressure and resistance in the pulmonary artery are normal. Normal haemodynamic conditions after operation cannot, on the contrary, be achieved in patients with a shunt through a ventricular septal defect, as long as this defect remains. Development of vascular changes in the lungs makes the cases more complicated. Consequently, when a ventricular septal defect is present, complete correction at the same session is indicated, in order to create as satisfactory conditions as possible.

In four such cases in which complete correction was performed in one session, the patients died shortly after operation. Death was due partly to a technical error, with overloading of the pulmonary circulation, and in one case was probably to be ascribed partly to right ventricular failure. After improvements in the technique, this method of operation seems, however, to offer good prospects of success even in cases with coincident ventricular septal defect.

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responded to that in the pulmonary artery.

In the venous atrium, a systolic rise in pressure up to 9 mm Hg was present, whereas the *a* wave was low (Fig. 4). The shape of the curve was atypical.

At a subsequent *angiocardiographic examination*, the contrast medium was injected into the newly created venous atrium, whence a reflux took place to both caval veins (Fig. 5). The reflux to the inferior vena cava was most marked. Both caval veins were displaced in an arch to the left, and opened into the small venous atrium, situated on the left. No stenosis was present at the opening of the caval veins into the atrium. The contrast medium passed without hindrance through the mitral valve into the left ventricle, which was still moderately dilated and somewhat more thin-walled than normal. The pulmonary orifice, pulmonary arteries and pulmonary veins had the same appearance as before operation. The pulmonary veins joined into a common trunk, corresponding to the posterior part of the left atrium (Fig. 6), which communicated with the anterior part of the right atrium. No impediment to passage could be demonstrated. The new arterial atrium lay behind the venous atrium and on its right, as can be inferred from Fig. 6. The right ventricle was less hypertrophied and dilated than before operation, whereas the appearance of the aorta was unchanged.

DISCUSSION

Operation has resulted in complete functional correction of transposition of the great vessels, in that all venous blood is directed to the pulmonary artery, and all arterial blood to the aorta. However, as before operation, the right ventricle works with abnormally high pressure (pressure in systemic circuit), and the left ventricle with abnormally low pressure (pressure in pulmonary circuit).

The anatomy of the atria has been changed by operation. Thus, the venous atrium now consists of part of the right atrium and the anterior part of the left atrium. The arterial atrium is formed by the posterior part of the left atrium and anterior part of the right atrium. Angiocardiographic examination showed the venous atrium to be small, and the two caval veins to be fairly markedly displaced in its direction. In view of the greatly altered anatomy, an impediment to emptying could easily have been expected, both at the site of suture between the caval veins and the arterial atrium, and in the atrial septal defect created, which forms the communication between the caval veins and the venous atrium. No signs of stenosis or an emptying impediment of any functional importance could be demonstrated at catheterization (Table I) or angiocardiography.

The systolic rise in pressure in the venous atrium (Fig. 4) probably does not imply any regurgitation through the mitral valve, especially as a systolic murmur is lacking. It may have been due to the catheter lying close to the valvular plane on recording, and to the fact that this venous atrium is small, and a considerable rise in pressure is therefore elicited even by an inappreciable increase in volume. Displacement of the

mitral leaflets towards the atrium during isometric contraction may imply a relatively appreciable narrowing of the space.

The arterial atrium, which has a considerably larger volume than the venous atrium, also consists of two communicating chambers without signs of stenosis (Fig. 6, A–B). Its emptying ability also seems to be good (Fig. 6, C–D). The low pressure in the pulmonary artery is a further indication of the efficient function of the arterial atrium. Thus, operation seems to have produced good results from the haemodynamic point of view.

Patients with intact ventricular septum and a mixed shunt at the atrial level are the ideal cases for this type of operation. This is because pressure and resistance in the pulmonary artery are normal. Normal haemodynamic conditions after operation cannot, on the contrary, be achieved in patients with a shunt through a ventricular septal defect, as long as this defect remains. Development of vascular changes in the lungs makes the cases more complicated. Consequently, when a ventricular septal defect is present, complete correction at the same session is indicated, in order to create as satisfactory conditions as possible.

In four such cases in which complete correction was performed in one session, the patients died shortly after operation. Death was due partly to a technical error, with overloading of the pulmonary circulation, and in one case was probably to be ascribed partly to right ventricular failure. After improvements in the technique, this method of operation seems, however, to offer good prospects of success even in cases with coincident ventricular septal defect.

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responded to that in the pulmonary artery.

In the venous atrium, a systolic rise in pressure up to 9 mm Hg was present, whereas the *a* wave was low (Fig. 4). The shape of the curve was atypical.

At a subsequent *angiocardiographic examination*, the contrast medium was injected into the newly created venous atrium, whence a reflux took place to both caval veins (Fig. 5). The reflux to the inferior vena cava was most marked. Both caval veins were displaced in an arch to the left, and opened into the small venous atrium, situated on the left. No stenosis was present at the opening of the caval veins into the atrium. The contrast medium passed without hindrance through the mitral valve into the left ventricle, which was still moderately dilated and somewhat more thin-walled than normal. The pulmonary orifice, pulmonary arteries and pulmonary veins had the same appearance as before operation. The pulmonary veins joined into a common trunk, corresponding to the posterior part of the left atrium (Fig. 6), which communicated with the anterior part of the right atrium. No impediment to passage could be demonstrated. The new arterial atrium lay behind the venous atrium and on its right, as can be inferred from Fig. 6. The right ventricle was less hypertrophied and dilated than before operation, whereas the appearance of the aorta was unchanged.

DISCUSSION

Operation has resulted in complete functional correction of transposition of the great vessels, in that all venous blood is directed to the pulmonary artery, and all arterial blood to the aorta. However, as before operation, the right ventricle works with abnormally high pressure (pressure in systemic circuit), and the left ventricle with abnormally low pressure (pressure in pulmonary circuit).

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Coarctation of the Aorta in Infants: Diagnosis and Operability

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Coarctation of the aorta, which was first treated surgically by Crafoord in 1945, belongs to the group of congenital heart diseases in which surgical treatment may be life-saving and curative, especially during the first few months of life. The increasing interest taken in the diagnosis of the types of congenital heart disease in infancy has revealed that more than half of the patients with coarctation of the aorta present symptoms in infancy. In addition, it appears that, if patients with early symptoms are left untreated, the prognosis is very grave. Thus, Keith found a mortality rate of 60–90 %, depending on the type of the cardiac defect.

MATERIAL

Since 1955, a total of 266 infants with severe congenital heart disease have been examined and treated in the Queen Louise Children's Hospital at Copenhagen; of these, 20 suffered from coarctation of the aorta. An account of the diagnosis and the results of treatment is given below. The methods of examination have previously been considered by Boesen (1956).

According to the operative and/or autopsy findings, the coarctations considered here may be divided into 6 types as shown in figure 1. This classification is very similar to that suggested by Keith, who distinguished between one postductal and three preductal types. In the series considered by Keith, the frequency of patent ductus arteriosus and intracardiac defects increased from the postductal through the three preductal types; patent ductus was thus present in 36 and 95 % and intracardiac defects

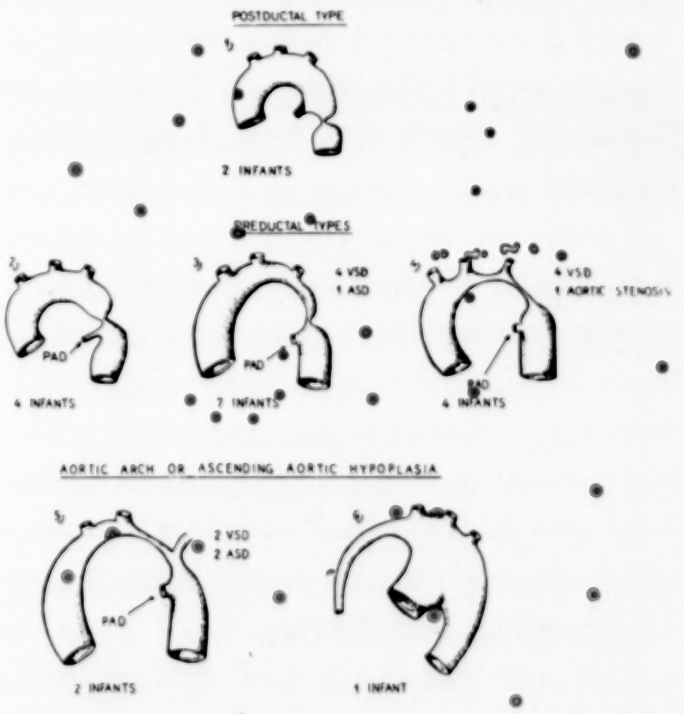


FIG. 1. Distribution of types 1 to 6 of coarctation of the aorta in 20 infants (operative and/or autopsy findings). Types 1 and 2 correspond to the adult type, type 3 to an intermediate type, and types 4, 5 and 6 to the infantile type.

MUSTARD, W. T., CHUTE, A. L., KEITH, J. D., SIREK, A., ROWE, R. D. & VLAD, P.: The surgical approach to transposition of the great vessels with extracorporeal circuit. *Surgery*, *36*: 39, 1954.

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TABLE 2. Relation between pulsation of the femoral arteries and the type of coarctation.

Type of coarctation	No. of cases	Pulsation of femoral arteries Present	Absent
Adult	6	0	6
Intermediate	7	1	6
Infantile	7	7	0
Total	20	8	12

From these observations it may be concluded—obviously with some allowance being made for the limited number of cases—that *absence of pulsation of the femoral arteries provides strong evidence in favour of an operable form of aortic coarctation*. This criterion seems to be so unquestionable that it may be permissible to perform exploratory thoracotomy with a view to operation for coarctation if pulsation of the femoral arteries is absent (while pulsation is distinctly palpable in at least the right radial artery), and if the condition is so serious that farther investigations cannot be awaited, but operation is vitally indicated (cf. Keith, page 189).

A diagnosis based on the demonstration of a significant difference in the blood pressure in the (right) arm and the legs is so certain that it is usually unnecessary to perform heart catheterisation and/or angiocardiography to obtain further confirmation. However, if a differential diagnosis as to the type of coarctation is desired, angiocardiography is required, and the type will then undoubtedly be most clearly visualised by aortography. In some cases, sufficiently definite information may be obtained by injection of contrast medium into the right side of the circulation; this is simpler than aortography, at least in infants, and offers the advantage that the simultaneous heart catheterisation may give information of complicating cardiac defects. Table 3 shows the diagnostic results obtained in the present series by angiocardiography with a view to visualisation of the coarctation and its type. It appears that injection into a peripheral vein did not give sufficient contrast density in the aorta for its evaluation in any of 3 cases. Injection into the right atrium was performed in 3 cases, all of infantile type, and gave satisfactory information, because all three patients had a ventricular septal defect with a right-to-left shunt, for which reason the ascending aorta was visualised before the contrast medium had passed through the pulmonary circulation, which results in a dilution of the medium. Injection into the pulmonary artery was performed in 13 cases, giving satisfactory results in 8. It should be noted that in 3 cases the examination was performed by means of a cinematograph with a 35 mm film; the diagnosis was made only in 1 case (adult type), but failed in 2 (1 adult and 1 infantile type), because the film size used seemed to be too small for a definite evaluation of the fine changes in the aorta. The remaining 10 were studied by means of our usual equipment for angiocardiography (Schonander); the results were satisfactory in 7, but not in 2 cases of adult type and in 1 case of intermediate type. In the cases in which satisfactory visualisation of the aorta is not obtained by injection of the contrast medium into the pulmonary artery, this is due to very slow passage of the medium

in 14 and 40 %, respectively, in the two groups—a tendency which is also reflected in the present series.

In a classification of the types with a view to the technical possibilities of operation the following groups may be used: (1) operable, (2) usually operable, possibly in connexion with the use of a graft, and (3) scarcely operable. This classification is very similar to that originally suggested by Bonnet, with an "adult" type (always technically operable) and an "infantile" type with an elongated hypoplasia of the aortic arch, which is nearly always inoperable. However, there is also an intermediate type with a shorter or longer, prestenotic hypoplastic portion of the aortic arch; this type may usually be resected, but may require grafting. As it is the task of the diagnostician to disclose which of these three possibilities is present in a given case, this series was analysed on the basis of this classification, the types 1 and 2 in figure 1 being designated as "adult type," the types 4, 5 and 6 as "infantile type" and type 3 as "intermediate type".

Patent ductus arteriosus was found in 4 of 6 cases of adult type, in 6 of 7 cases of the intermediate type, and in all 7 cases of infantile type. Ventricular septal defect was absent in all 6 of adult type, but present in 4 of the 7 of intermediate type and in 6 of the 7 of infantile type, of which one showed hypoplasia of the left ventricle and atrium.

The age distribution of the patients with the various types of coarctation is shown in Table 1. It appears that 13 of the 20 patients were examined before they were 6 months old. It should be noticed that all the patients in the series presented symptoms of insufficiency, usually in a pronounced degree.

TABLE 1. Distribution by age and type of coarctation revealed in the examination of the 20 patients.

Age, months	No. of cases	Type of coarctation: Adult	Intermediate	Infantile
0–2	11	3	6	2
3–5	2	—	—	2
6–13	7	3	1	3
Total	20	6	7	7

CLINICAL AND RADIOGRAPHIC APPEARANCE

In making a clinical diagnosis of coarctation of the aorta, the demonstration of a blood-pressure difference between the arms and legs is of decisive significance. In practice, this is usually done by studying whether pulsation of the femoral arteries is present or not, since absence of pulsation provides strong circumstantial evidence in favour of coarctation. However, it is a well-known fact that coarctation may be present even when pulsation of the femoral arteries is revealed; this may, for example, be the case in the presence of a patent ductus arteriosus opening distally to the stenosis of the aorta. The observations as to pulsation of the femoral arteries in the present series appear from Table 2. It is seen that pulsation was absent in all cases of adult type (in which 4 stenoses were preductal), while all 7 of infantile type showed pulsation; in the intermediate group, pulsation was observed in 1 of 7.

the right half of the circulation in association with heart catheterisation does not give definite diagnostic information.

Thus, whereas palpation of the femoral pulse and angiocardiography give decisive information as to the presence or absence of aortic coarctation and its type, conventional radiography and electrocardiography are of little value in the differential diagnosis between operable and inoperable types, as appears from Table 4. The radiographic findings were largely alike in the two groups. On the other hand, it may be noted, as a negative criterion, that the absence of ventricular hypertrophy and of right axis deviation weighs against a diagnosis of aortic coarctation of the inoperable type.

SURGICAL TREATMENT AND THE COURSE OF DISEASE

Of the 20 patients in the series, 4 died before operation. The remaining 16 were all subjected to operation. In 12 cases, resection of the coarctation with end-to-end anastomosis was performed (Table 5); of these, 5 died postoperatively from cardiac incompetence, which had also been present before the operation, manifested, *inter alia*, by pulmonary hypertension due to failure of the left ventricle. The two patients with the intermediate type who died after operation had both a ventricular septal defect. Of the non-resected patients, one died in relation to division of the patent ductus arteriosus, at which it appeared that the coarctation was technically inoperable. Three died after exploratory thoracotomy, which confirmed the pre-operative assumption of inoperability, but the operations were performed because the condition was so critical that the only chance of survival was that it would, in spite of everything, be possible to correct the coarctation.

TABLE 5. Course of disease or result of surgical treatment of coarctation of the aorta in 20 infants.

Type of coarctation	No. of cases	Subjected to operation		Not subjected to operation
		Died	Survived	Died
Adult	6	1	3	2
Intermediate	7	2	4	1
Infantile	7	6[a]	—	1

[a] Three died after exploratory thoracotomy, two after resection of the coarctation, and one after resection of a patent ductus arteriosus.

The 4 patients who were not subjected to operation were all under 2 months of age, and death occurred on the first or second day in hospital. (One of infantile type was considered inoperable; death occurred 6 months later.)

In all cases the indication for operation was pronounced cardiac incompetence. Consistent, pre-operative digitalis therapy was not given, mainly because surgical treatment was considered to offer the only possibility of relieving the patients of the severe state of cardiac incompetence.

PRE-OPERATIVE EVALUATION OF THE PROGNOSIS

By a comparison of the course of the disease and the clinical observations and the results of certain investigations performed in this series (Table 6) it is possible fairly accurately to assess the prog-

TABLE 3. The reliability of the angiocardiographic diagnosis of coarctation of the aorta related to the site of injection of the contrast medium.

Type of coarctation	No. of patients studied	No. of angiocardiographic examinations	Satisfactory visualisation of the coarctation by injection of contrast medium into: Saphenous vein Yes	Saphenous vein No	Right atrium Yes	Right atrium No	Pulmonary artery Yes	Pulmonary artery No	Aortography Yes	Aortography No
Adult	6	6	—	1	—	—	3	2	—	—
Intermediate	7	9	—	1	—	—	3	2	3	—
Infantile	7	8	—	1	3	—	2	1	1	—
Total	20	23	—	3	3	—	8	5	4	—

through the pulmonary circulation caused by insufficiency of the left ventricle with "backward-failure"; the systolic pressure in the pulmonary artery in the 3 unsatisfactory cases was 76, 90 and 62 mm Hg, respectively; the PVC was not measured.

Aortography was performed in 4 patients and resulted in definite and distinct visualisation of the site and extent of the coarctation. In recapitulation, it may be said that if an attempt is made to obtain the best possible visualisation of the coarctation by angiocardiography with injection of the contrast medium into the right half of the circulation, the injection should preferably be given into the pulmonary artery; the chances of a satisfactory result are reduced in the presence of insufficiency of the left ventricle with slow passage through the pulmonary circulation. Injection into the right ventricle gives the information required if a ventricular septal defect with (partial) right-to-left shunt is present. Injection into a peripheral vein cannot be recommended. Consequently, we have adopted the procedure, if coarctation is suspected, that we primarily aim at injection into the pulmonary artery and employ aortography only if the angiocardiography with injection into

TABLE 4. Relation between type of coarctation and radiographic and electrocardiographic findings.

Abbreviations: RAD, right axis deviation; RVH, right ventricular hypertrophy.

Type of coarctation	No. of cases	Cardiothoracic index ⩾0.60	Increased pulmonary vascularity	RAD	RAD + RVH	RAD + combined hypertrophy
Adult	6	3	3	2	2	—
Intermediate	7	7	4	5	3	2
Adult + intermediate	13	10	7	7	5	2
Infantile	7	5	4	7	4	3

ductus was revealed by catheterisation of the ascending aorta through the ductus. Angiocardiography of the 17 patients with patent ductus arteriosus revealed this anomaly only in 8, including 2 with a left-to-right shunt. As previously stated, the prognosis is poor in the presence of a right-to-left shunt; as angiocardiography appears to be a reliable diagnostic aid for its demonstration, this method of examination is of very great value also from this point of view in the study of infants with coarctation of the aorta. The explanation why only 10 of the 17 cases of patent ductus were revealed pre-operatively may partially be that the ductus did not function at the time of the examination.

As previously pointed out, ventricular septal defect was present in 10 of the 20 patients; the defects were recognised during life in all 10 patients. In 5 of the patients, suspicion of the defect was aroused by auscultation, which revealed a systolic murmur, at least of grade III, at the lower left sternal border. In 7, the defect was revealed by oxygen analyses in relation to heart catheterisation; these showed a difference in the oxygen content of the blood from the right atrium and from the right ventricle amounting to at least 1 vol%. Among the 9 patients with ventricular septal defect subjected to angiocardiography, this revealed the defect in 7; the demonstration was based both on a partial right-to-left shunt between the ventricles and on the presence of re-circulation of contrast medium to the pulmonary artery from the left ventricle. From these observations it must be concluded that it is possible with great certainty to recognise a ventricular septal defect associated with coarctation, because both auscultation, heart catheterisation and angiocardiography contribute fundamentally to the diagnosis. As the prognosis is markedly aggravated if coarctation of the aorta is associated with a ventricular septal defect, it is very important to reveal its presence; 9 of the 10 patients with septal defects in the present series succumbed.

SUMMARY

Coarctation of the aorta was diagnosed in 20 of 266 infants with severe congenital heart disease seen in the Queen Louise Children's Hospital.

The 20 cases of coarctation may be divided into 6 types, comprising postductal and preductal types and hypoplasia of the aortic arch. With a view to operability they may be classified in three groups, viz. operable, usually operable, and scarcely operable, closely corresponding to the classic adult type (types 1 and 2), an intermediate type (type 3) and the infantile type (types 4, 5 and 6).

Of the 20 infants, 13 were under 6 months of age, the intermediate type showing a preponderance during the first 6 months of life.

Absence or presence of pulsation of the femoral arteries and angiocardiography with injection of the contrast medium into the pulmonary artery were the most important diagnostic aids for the recognition of the type of coarctation. In the evaluation of the operability, the absence of pulsation of the femoral arteries is of great importance. Conventional radiography and electrocardiography are not of decisive significance in the diagnosis.

Radical operation with resection of the coarctation was performed in 12 of the 20 infants; 4 were of the adult type, 6 of the intermediate type, and 2 of the infantile type. Fatal outcome was seen in 1 case of adult type, in 2 of intermediate type and in 2 of infantile type.

The analysis shows that patients who have ventricular hypertrophy, enlarged heart, a systolic pressure in the right ventricle exceeding 40

TABLE 6. Relation of the prognosis to a number of symptoms and objective findings in 20 infants with coarctation of the aorta.

	No. of cases	Deaths
Electrocardiographic findings		
Extremity leads		
No axis deviation	4	0
Right axis deviation	14	11
Left axis deviation	1	1
Precordial leads		
No hypertrophy	3	0
Right ventricular hypertrophy	11	7
Combined hypertrophy	5	5
T V_{5-6} negative	2	2
Extremity and precordial leads		
Right axis dev. + right ventricular hypertrophy	9	6
No axis deviation, no hypertrophy	3	0
Clinical findings		
Tachypnoea	15	11
Cyanosis	5	5
Poor weight gains	14	10
Enlarged liver ($\geq$1.5 cm below costal margin)	9	7
Radiographic findings		
Index < 0.60	4	3
Index ≥ 0.60	16	10
Normal lung fields	9	4
Increased vascularity	11	9
Index < 0.60, normal lung fields	3	1
Systolic pressure in right ventricle		
Below 40 mm Hg	4	0
40 mm Hg or over	14	11
Appearance of symptoms of insufficiency		
Within first month of life	15	12
After first month of life	5	1

nosis. As might be expected, normal electrocardiogram, normal radiographic findings and a normal systolic pressure in the right ventricle give the best outlook, whereas patients with ventricular hypertrophy, enlarged heart, pulmonary congestion, tachypnoea, cyanosis, enlarged liver and a systolic pressure in the right ventricle of at least 40 mm Hg in whom the symptoms of insufficiency become manifest shortly after birth have the poorest prognosis.

COMPLICATING CARDIAC DISEASE

As already mentioned, patent ductus arteriosus was present in 17 of the 20 patients. It is insignificant for the surgeon to know beforehand if the ductus persists, and it is presumably also without prognostic importance whether or not this anomaly is associated with a left-to-right shunt. On the other hand, it is of crucial importance to ascertain pre-operatively if a patent ductus is associated with a right-to-left shunt, as this means a considerable aggravation of the prognosis and often, if not always, represents a contra-indication to closure of the ductus as an isolated surgical measure. A right-to-left shunt through a patent ductus arteriosus or through a ventricular septal defect was demonstrated pre-operatively in 6 of the patients; all these patients died. Incidentally, only 10 of the 17 cases of patency of the ductus arteriosus were demonstrated pre-operatively. Only in 1 case was a typical continuous murmur audible. In 3 cases the patency of the

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Coarctation of the Abdominal Aorta

Case Report and Description of Successful Surgical Treatment

J. Hanson, D. Ikkos, L. Johansson, U. Rudhe and Å. Senning

Coarctation of the abdominal aorta is a rarely diagnosed condition, only 25 cases having been reported in the literature up to February 1958 (Depraz, 1953; Gerbasi, Kibler & Margileth, 1958; Guastarino & Becu, 1956; Martin & Yount, 1956; Tawan Sarawongse Gunnag, 1957). In nine of these in which the diagnosis was made during life, surgery was attempted, but only three results have been reported as successful (Gerbasi, Kibler & Margileth, 1958). In two cases in which the origin of the celiac axis and renal arteries was from the coarcted segment, a by-pass homograft was used.

The present report is concerned with a case of abdominal aortic coarctation involving the celiac axis and renal arteries, and describes a new surgical approach which was employed successfully.

CASE REPORT

L. W., a 12-year-old white female, was seen in the Pediatric Outpatient Clinic with a 2-year history of headache and dizziness associated with physical exertion and excitement. Associated complaints consisted of paresthesias of the fingers, frequent nervousness and inability to keep up with schoolwork. There were no symptoms of claudication in the legs. Remainder of the past history, family history and review of symptoms were non-contributory. Examination at that time revealed blood pressure to be 175/100 in the arms, vital signs otherwise normal. A weak systolic murmur was heard over the apex of the heart. The lungs were clear. Femoral pulses were not palpable and a diagnosis of aortic coarctation was entertained.

The patient was admitted to the hospital one week later for complete investigation. At that time her body build was seen to be normal for her age. Weight 83 lbs, height 59 inches. Secondary sex characteristics had not yet appeared. Café au lait spots were noticed over the anterior and posterior aspects of the torse. Blood pressure was 200/130 in the arms, and the femoral pulses were not palpable. Blood pressure at the arms, and the femoral pulses were not palpable. Blood pressure at the legs taken by the flush

mm Hg and symptoms of insufficiency from birth have the poorest prognosis.

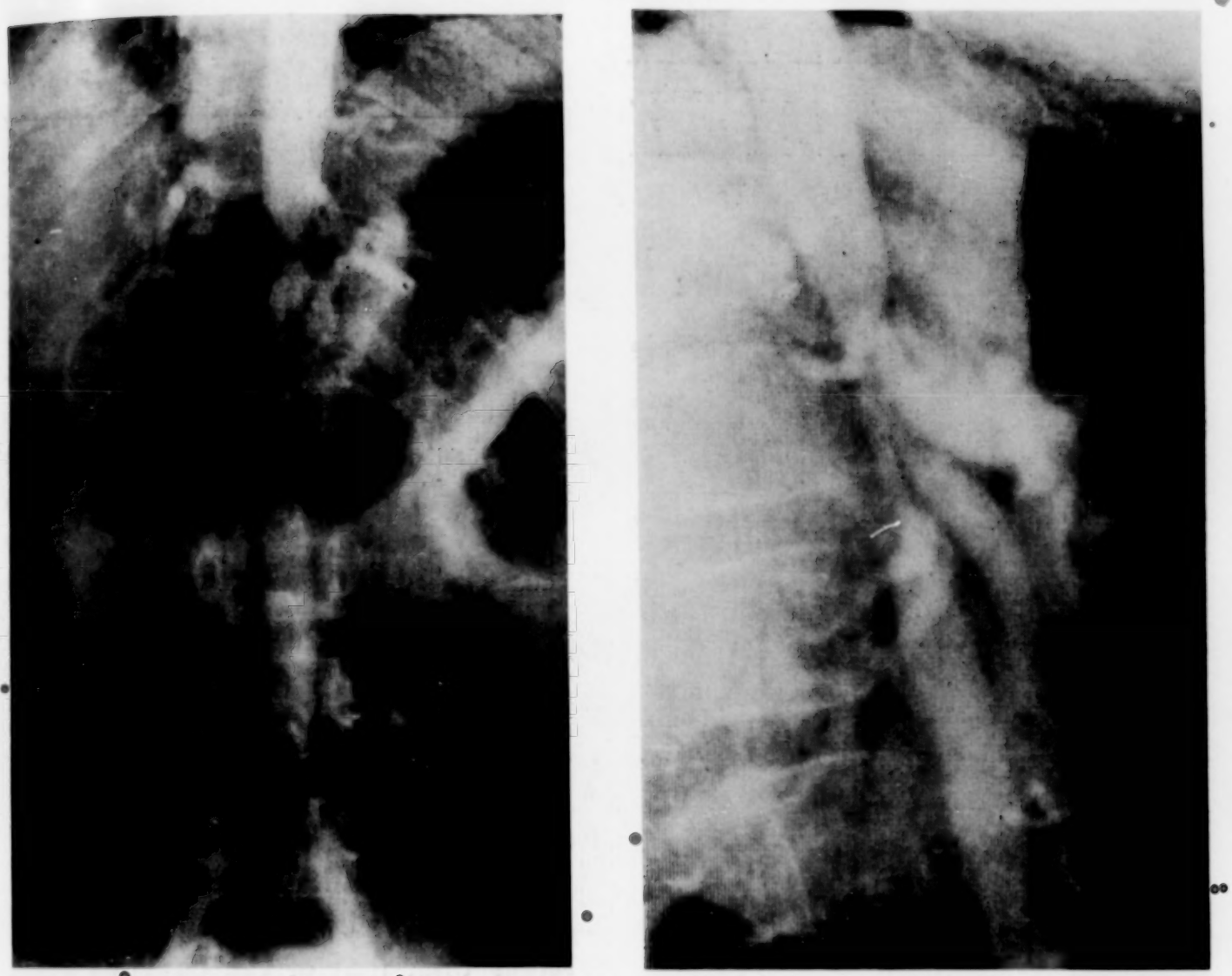
Patent ductus arteriosus was present in 85 % and ventricular septal defect in 50 % of the patients. These complicating cardiac conditions aggravate the prognosis; death occurred in 9 of the 10 patients with ventricular septal defect and in all patients with a right-to-left shunt referable to a patent ductus arteriosus or to a ventricular septal defect.

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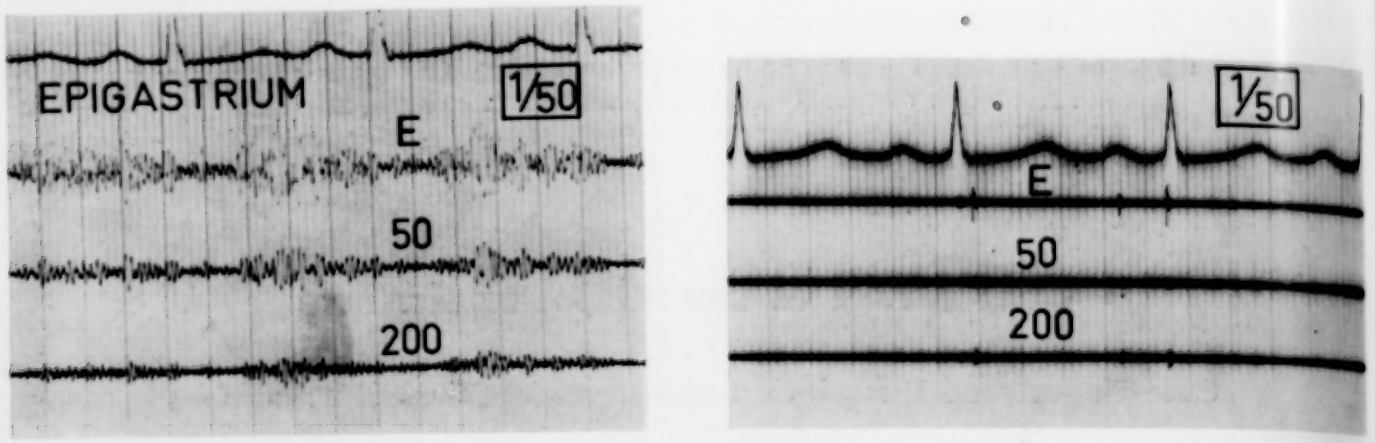
A B

FIG. 2. Coarctation of the abdominal aorta. *A*. frontal view. *B*, lateral view; the constriction of the aorta affects the segment from which the celiac, superior mesenteric and renal arteries emerge.

hiatus aorticus and continuing below the diaphragm was revealed. The length of the constriction was 6 cm. The most stenotic portion of the affected segment had a calibre of 4 to 5 mm and a length of 4 cm. The celiac artery as well as the superior mesenteric artery and the renal arteries took off from this highly stenotic portion. The left renal artery was narrow, measuring about 4 mm in width. The right renal artery was slightly wider. The diameter of the aorta below the constriction was 13 mm. There was no pre- or poststenotic dilatation of the aorta. Tortuous and dilated intercostal, lumbar and epigastric arteries were involved in the collateral circulation.

Laboratory data (see Table I): All examinations were within normal limits with the exception of a marked hypercholesterolemia. Determinations carried out on the patient's parents revealed values of 528 mg % in the mother and 361 mg % in the father.

The combined results of the physical, radiological and laboratory examinations thus established the diagnosis of coarctation of the abdominal aorta. Because of rapid progress of the patient's symptoms some form of corrective surgery seemed urgent. The operation was done 3 months after the initial study.



A B

FIG. 1. Phonocardiogram over the epigastrium. *A*, preoperative: typical continuous murmur. *B*, postoperative: absence of any murmur.

method was ca. 125 mm Hg systolic. The cardiac apical beat was somewhat heaving in character in the 5th left ICS in the midclavicular line. A slight systolic murmur of Grade II–III was again heard over the entire precordium with a maximum in the 3rd left ICS. The 2nd sound over the 2nd right ICS was split with accentuation of the 1st component. Palpable intercostal artery pulsations were detected over the back bilaterally and in these same regions a continuous murmur was heard. There was no cyanosis, clubbing or edema. Palpation of the mid-epigastric region revealed a continuous thrill in the midline. Auscultation over this region demonstrated the presence of a continuous murmur of Grade IV. The abdominal aorta was not palpable below the level of the umbilicus. Examination of the abdomen was otherwise negative, the liver being nonpalpable.

The preliminary clinical diagnosis at this point was coarctation of the abdominal aorta.

Electrocardiogram: Electrical axis +25°. Signs of mild left ventricular hypertrophy with ST segment depressions in Leads V_4–V_7.

Phonocardiogram: confirmed the clinical findings (see Fig. 1 *A*).

Oscillography: Preoperatively oscillations in the arms were large and free with a maximum of 120–100 mm, while those in the legs were small and showed a maximum of 100–80 mm.

Exercise test performed on the bicycle ergometer showed that the patient had a reduced working capacity for her age (300 kgm/min.). The blood pressure in the arms during this test increased from 185/135 to 205/165 mm Hg.

Radiological examination of the chest: The configuration of the heart was normal. No abnormality of the mediastinum or of the great vessels was found. The heart volume, related to the surface area of the body, was 400 cc, indicating a moderate enlargement of the heart. The vascularity of the lungs was normal. Small notching of the ninth rib was noted on the left and the right side.

Angiocardiography: Figs. 2 *A* and *B*. Following heart catheterization, which revealed normal findings for the right side of the heart, 42 ml of a 70 % solution of Urokon was injected into the pulmonary artery via the catheter. A constriction of the aorta at the level of the

two weeks following surgery. Two months later she was re-admitted to the hospital for follow-up studies. She had remained entirely symptom-free during the interval at home except for slight abdominal pain associated with rapid walking. Headaches, dizziness and paresthesias had disappeared.

Examination revealed blood pressure in the arms to be 135/100 and in the legs 170/110 mm Hg by auscultation. Intercostal pulsations were no longer felt. A very weak systolic murmur, Grade I–II remained over the entire precardium.

The continuous thrill and murmur over the epigastrium had disappeared, and the abdominal aorta was now palpable.

Electrocardiogram: unchanged from the preoperative recording.

Phonocardiogram: confirmed absence of any murmur over the abdomen (see Fig. 1*B*).

Oscillography showed lower-amplitude oscillations in the arms than preoperatively and markedly increased oscillations in the legs. The entire examination was now interpreted as being normal.

Radiological examination of the chest: The relative heart volume was estimated to 300 ml. The reduction in relative heart size since the time of operative intervention was 100 ml.

Retrograde aortography: Fig. 3. A polyethylene catheter no. 205 was introduced into the femoral artery according to the Seldinger technique (Seldinger, 1953). The tip of the catheter was inserted into the middle part of the thoracic aorta. 28 ml of a 60 % solution of Renographin was injected and the abdominal aorta was depicted in serial frames in the frontal and lateral projections. There was no longer any hindrance to passage in the previously constricted segment. The aorta was slightly deformed at this level as was revealed by a moderate bulge of its left aspect as well as a slight remaining flattening of the wall along its sagittal axis. The corresponding diameters were 18 and 10 mm respectively. The renal arteries had increased in width and measured 5 to 6 mm in diameter. There was a marked regression in calibre



FIG. 3. Appearance of the aorta after relief of the obstruction. Slight deformity of the vessel with a bulging left lateral aspect at the site of surgical correction. Increased width of the renal arteries. Diminished tortuosity and size of the collaterals.

TABLE 1

Examination	Preoperative	Postoperative, 2 months
Hb. g %	13.1	13.0
WBC	3.600	4.200
S.R.	16 mm	5 mm
Urinalysis	Normal	Normal
Creatinine clearance	141 ml/min/1.73 m²	136 ml/min /1.73 m²
PAH clearance	560 ml/min/1.73 m²	488 ml/min /1.73 m²
Inulinclearance	128 ml/min/1.73 m²	—
Water-loading	Sp. gr. 1.004–1.035	Sp. gr. 1.004-1.035
Exercise tolerance	200 kg/min	200 kg/min
Heart volume	400 cc/m²	300 cc/m²
Total serum cholesterol	389–449 mg %	358 mg %
ester	236 mg %	
free	213 mg %	
Bilirubin	0.2 mg %	
Thymol turbidity test	2.8 units	
Total serum protein	7.9 %, Alb. 62.8 %	
	Globulin α_1 3.9	
	α_2 9.9	
	β 6.7	
	γ 16.7	
PBI	5.5 %	
Wasserman	Neg.	

SURGICAL CORRECTION

Longitudinal aortotomy and insertion of a homologous frozen dried arterial graft under hypothermia. External cooling by Persson–Jack Adams Ray–Heljestrand cooling apparatus.

Thoracoabdominal incision at IC 8. The aorta was stenosed for a length of 6 cm, from 2 cm above the diaphragm to 3 cm below. The celiac artery, the superior mesenteric and both renal arteries originated from the constricted part of the aorta. The aorta and the origin of the arteries were constricted by abundant fibrous adventitial tissue. The aortic wall was fibrous and hard. The tissue was dissected away and by means of this dissection the arteries were considerably widened. The left renal artery was 3 mm in diameter and the right about 5 mm in diameter at the origin before the dissection. After the adventitial tissue had been cleaned away their diameter increased to 5–6 and 7–8 mm respectively. Two pairs of intervertebral arteries were dissected and tied at the coarctation. Two pairs of intervertebral arteries above and below the coarctation were dissected and occluded by means of sling ligatures. The aorta was clamped above and below the coarctation. The celiac, superior mesenteric, and both renal arteries were occluded by sling ligatures. The aorta was longitudinally incised over the coarctation and further up and down until it was of normal width. An 8 cm long homologous aortic graft with a diameter about one third larger than that of the patient's aorta above the coarctation was split lengthwise whereupon the graft was pointed at the ends. The graft was then sutured into the longitudinal incision in the patient's aorta with a single row of over and over suture. In this way the coarctation was widened from a diameter of about 4–5 mm to about 20 mm. When the circulation was re-established the arteries leaving the area of coarcation seemed to have normal width even at their origin from the aorta. Re-warming of the patient was begun during suture of the thoracoabdominal wound.

FOLLOW-UP EXAMINATIONS

The patient's postoperative course was uneventful and she returned home

In those cases presenting involvement of the renal arteries a preoperative evaluation of renal function is also to be advised. The results of these investigations may well have a bearing on the type of surgical repair attempted.

The question has previously been discussed by many authors whether the hypertension of aortic coarctation is partially due to generalized arteriolar constriction as in essential hypertension. Renal function studies in the present case by means of inulin and PAH clearances produced normal filtration fraction figures. This is therefore in agreement with the opinion of others (Culbertson, Eckstein, Kirkendall & Bedell, 1957; Ikkos, Wallgren & Zetterqvist, 1959) who propose that the mechanical factor is the most important in the genesis of the hypertension found above the coarctation.

In general the operative procedure used in the present patient appears to be relatively simple technically, and from a functional standpoint produces an end-result which most nearly approximates normal conditions. As the graft was made about 30 % wider than the patient's aorta above the coarctation there will be no relative stenosis during the patient's further growth. Grafts sutured into the arteries by this technique seem to be as well tolerated, e.g. in the coronaries, as regular grafts (Å. Senning, unpublished data). Of perhaps greatest importance is the fact that this type of procedure *directly* increases blood flow to the renal arteries and celiac axis by relieving the vascular obstruction by dissecting away constricting fibrous tissue strangulating the arteries at the same time obviating any undue manipulation of these vessels. Other attractive features of this procedure include a short period of occlusion of the celiac and renal arteries during hypothermia, thus providing a margin of safety against the injurious effects of anoxia on hepatic and renal function.

From the clinical viewpoint the operative results have also been successful. Follow-up at 9 months postoperatively reveals complete disappearance of symptoms, marked decrease of blood pressure, normalisation of the ECG, and significant decrease of cardiac volume and collateral circulation on radiological examination.

Consideration of the possible etiology of coaretation of the abdominal aorta in the present case leads us to believe that it is a congenital malformation. Examination of the coarcted area at the time of operation did not reveal any evidence of a localized arteriosclerotic or inflammatory process. The hypercholesterolemia exhibited by the patient seems certainly to be a familial condition judging by the parents' high blood cholesterol values.

SUMMARY

A case of coarctation of the abdominal aorta involving the vessels of the celiac axis and the renal arteries in a 12-year-old girl is presented.

The value of careful physical examination and aortographic localization of the malformation preoperatively is stressed.

A new surgical repair with successful result is described.

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and tortuosity of the intercostal and lumbar arteries. A normal nephrographic effect was displayed on both sides.

The results of the postoperative examinations are shown (together with the preoperative ones) in Table 1. Clearance studies showed unchanged values when compared with the preoperative ones. Excretory urography, which was performed in direct connection to the aortography showed normal dye concentration as well as normal renal and ureteral structures. The patient was readmitted 9 months after the operation. She was symptom-free. The clinical as well as the other laboratory findings were unchanged, intra-arterial pressure from the brachial and femoral artery showed 142/89, and 142/96 mm Hg respectively. The ECG was normalized.

DISCUSSION

Since the pioneering work of Crafoord, the problem of an accurate and timely diagnosis of coarctation of the aorta has become of great interest not only from a theoretical, but also from a practical point of view. Experience teaches that a delayed diagnosis carries a less favorable prognosis, primarily with regard to the age of optimum operability and irreversible changes in arteries as a consequence of prolonged hypertension. Thus, early and correct diagnosis becomes not only desirable but necessary to bring the patient to the operating table with the best possible chances for a complete cure. In this regard the case presented here exhibited such rapid progression of the subjective symptoms that operative intervention was indicated much earlier than had been anticipated.

The general diagnostic unawareness associated with coarctation of the abdominal aorta is well emphasized in the previous descriptions of this abnormality. Although by far the vast majority of coarctations will be found in the usual high, thoracic position, unnecessary risk to the patient and superfluous operative procedures can be avoided in cases of abdominal coarctations by careful palpation and auscultation of the abdomen as well as the use of aortography preoperatively in suspected cases.

An unusual location of the constriction should be suspected, when in the presence of unequivocal clinical signs of coarctation of the aorta, the typical vascular deformity of the upper part of the mediastinum is lacking in conventional roentgenological examination of the chest.

The value of demonstrating preoperatively the exact location of the coarctation by contrast radiography cannot be overemphasized. The complicating anatomical relationships of the particular case are then known and intelligent planning of the entire operative procedure can be accomplished.

Operative or preoperative angiography has been employed in 11 cases of abdominal or thoraco-abdominal coarctation of the aorta (Depraz, 1953; Gerbasi, Kibler & Margileth, 1958; Guastarino & Becu, 1956; Martin & Yount, 1959; Tawan Sarawongse Bunnag, 1957). In our case the postoperative anatomy of the aorta was demonstrated by aortography as well. This disclosed complete abolition of the constriction, an increase in calibre of the renal arteries and anatomic regression of earlier collateral vessels.

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Congenital Hypoplasia of the Right Pulmonary Artery Associated with Myomatosis of the Lung

HARRY HERZENBERG, ULF RUDHE and BJÖRN I. IVEMARK

Absence or hypoplasia of a main branch of the pulmonary artery has been diagnosed in a rapidly increasing number of cases since Madoff, Gaensler & Strieder's report in 1952. About 60 cases have been recorded in the literature, approximately 20 having been examined by angiocardiography. Heart catheterization and pulmonary function studies have been performed in about 17 cases.

This report concerns an 11½-year-old boy with atresia of the right pulmonary artery associated with myomatosis and vascular abnormalities of the right lung.

CASE REPORT

An 11½-year-old boy was admitted to the Children's Clinic at Karolinska Sjukhuset because of repeated episodes of pneumonitis. Since the age of one year he had been treated in different hospitals for 15–20 bouts of bronchopneumonia located in the right lung. Bronchoscopy and bronchography performed at the age of 6 years revealed no abnormality. He never displayed any cyanosis and he experienced no dyspnea during the intervals free from infection. No hemoptyses had been noted.

Physical examination revealed a fairly pale slender boy in the lower normal limit of weight and height for his age. No cyanosis or dyspnea was present. There was no clubbing of the fingers and no liver enlargement. He had a slight cough. The femoral arteries were palpable. Blood pressure in the arms was 115/65. Heart rhythm was regular and no significant murmurs were heard or recorded. The second sound was abnormally split. Its components were not accentuated. The movement of the right hemithorax was diminished, the breath sounds were faint and there were crepitant râles heard over the right side.

Bronchospirometry: The minute volume of ventilation was 74 % of the total in the left lung and 26 % in the right lung. The oxygen consumption was 100 % in the left lung. No oxygen uptake could be demonstrated in the right lung.

Electrocardiogram showed incomplete right bundle branch block. There were no signs of hypertrophy.

Physical exercise test, performed on a bicycle ergometer, showed a working capacity of 300 kgm/minute when in the "steady state" and with a heart rate of 170. The capacity was somewhat low for the patient's age. The ventilation was approximately normal during rest and also during exercise. During the maximum working load an increase occurred in the respiratory frequency but not in the ventilation volume.

Electrocardiogram during work revealed ST and T changes and ventricular extrasystoles.

Roentgenology: Roentgenographic examination of the chest (Fig. 1) revealed a moderate underdevelopment of the right hemithorax and an equivalent distension of the left lung. There was

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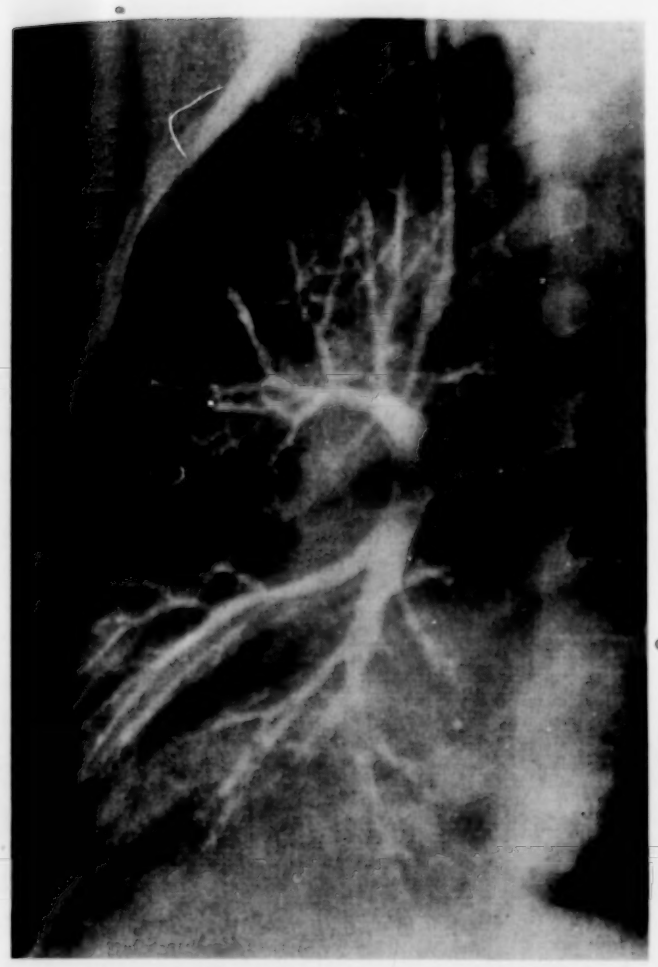


FIG. 2. The bronchogram of the right lung has a normal appearance.

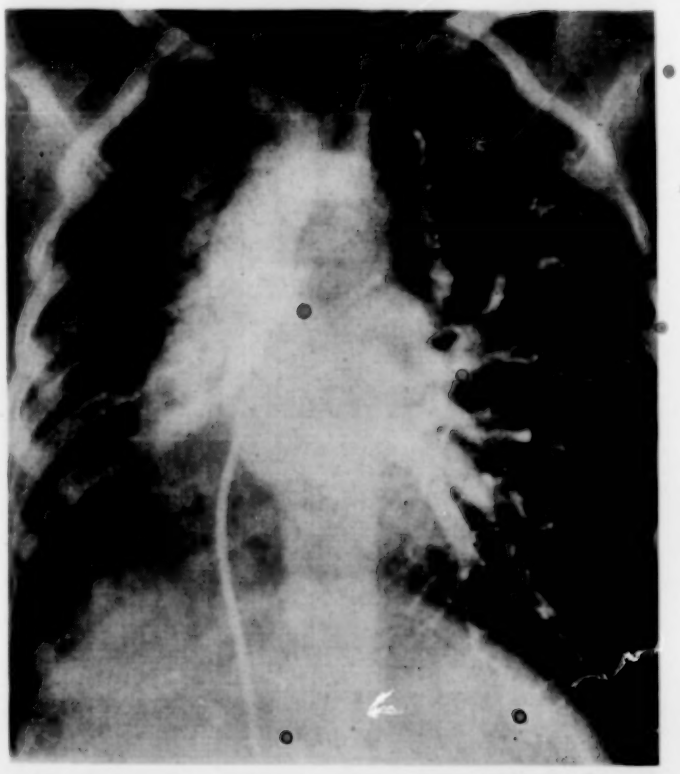


FIG. 4. Slight dilatation of the left pulmonary veins is found. The left atrium, left ventricle, and the aorta have the normal size and width. The heart is displaced to the right.

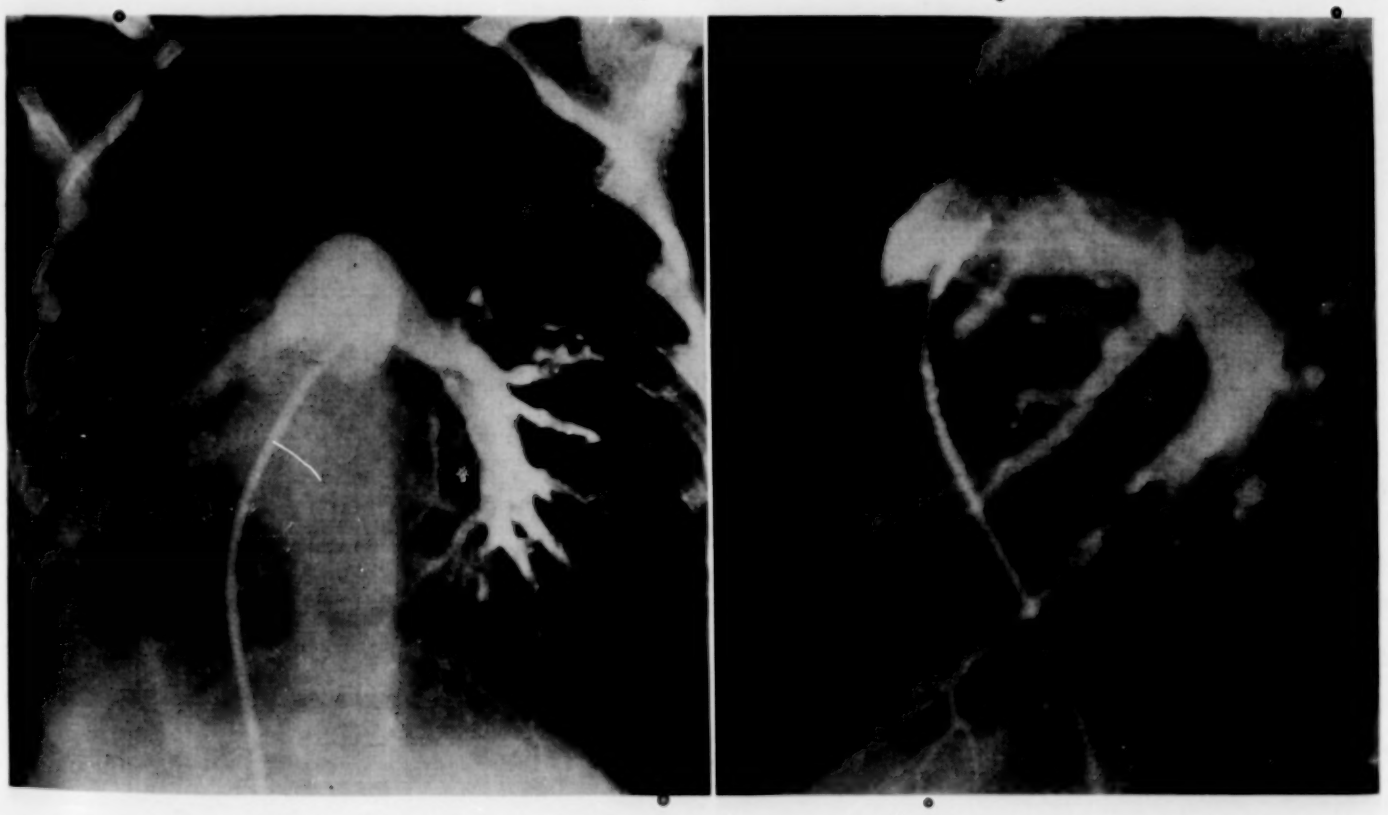


FIG. 3. The pulmonary arterial tree is outlined by contrast medium injected into the pulmonary artery trunk. The right pulmonary artery is short and narrow and forms a blind pouch. The left pulmonary artery and its branches are widened.

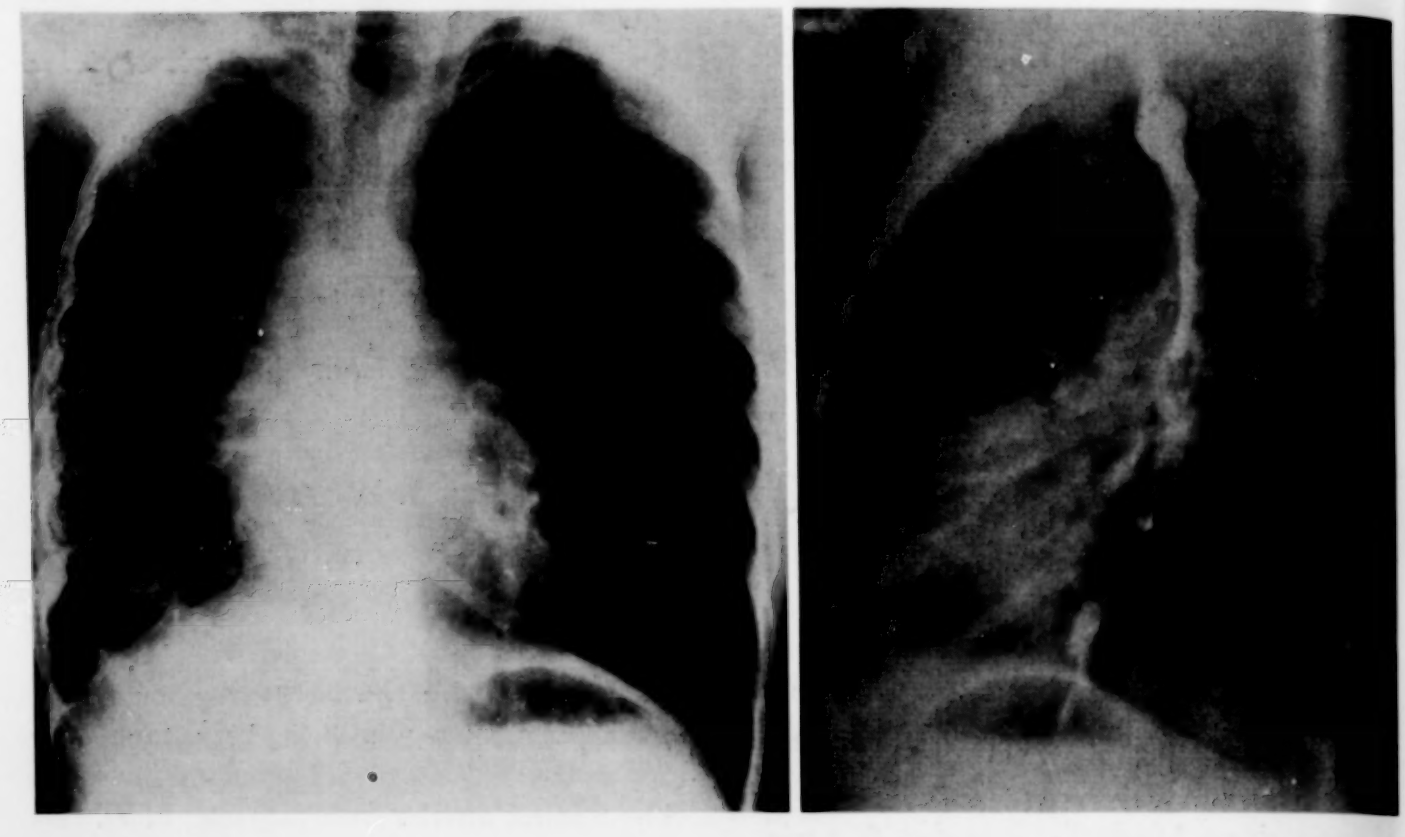


FIG. 1. The right hemithorax is smaller than the left, the mediastinum and the heart are shifted to the right. The left lung is distended. No pulmonary artery branches are seen in the right lung. The vascular markings consist of a network of small arterial collateral vessels. There is no true mediastinal herniation.

displacement of the mediastinum and the heart toward the right but no true herniation of the lung was present. The left pulmonary artery and its branches were widened indicating an increased blood flow. In the right lung there was markedly decreased vascularity and no right main branch could be identified. Numerous small, irregular vessels forming a lacy mesh-work highly suggestive of a collateral circulation were seen to extend throughout the lung. The vessels were particularly richly developed in the infero-medial parts. The outline of the hemidiaphragm was irregular at these sites. It was felt that the general density of the lung was more marked than could be attributed to its reduced size and to the extensive network of the collaterals. No confluent areas of consolidation were, however, noted. The lung was surrounded by a slightly thickened pleura. A review of earlier films revealed that this was the remnant of a pleurisy contracted six years earlier. The heart was of the normal size and shape. It was moderately shifted to the right.

Bronchography performed on the right side (Fig. 2) did not disclose anything abnormal. The branching of the bronchi was normal.

Heart catheterization was performed under local anesthesia from the right saphenous vein. The pressures in the right ventricle and in the main stem of the pulmonary artery were 34/3 ($m = 13$) and 33/10 ($m = 21$) mm Hg respectively. The right atrial mean pressure was 4 mm. Hg. The left pulmonary artery was easily entered with the catheter. As expected the catheter could not be inserted into the right lung. The mean pressure in the pulmonary wedge position was 7 mm Hg and the oxygen saturation there was 100 %. Systemic arterial saturation measured after puncture of the femoral artery was 97 %. No shunt was detected.

Angiocardiography: This was performed selectively by injecting 25 cc of a 70 % solution of sodium acetrizoate (Rheopak, Astra, Sweden) into the main stem of the pulmonary artery via a catheter introduced from the saphenous vein. The pulmonary artery was of normal size but the right main branch was narrow and short and was outlined only in its first 2 cm, where it was seen to be severely stenosed to a degree amounting to atresia (Fig. 3). The pulmonary veins (Fig. 4), which entered the left atrium, were well filled

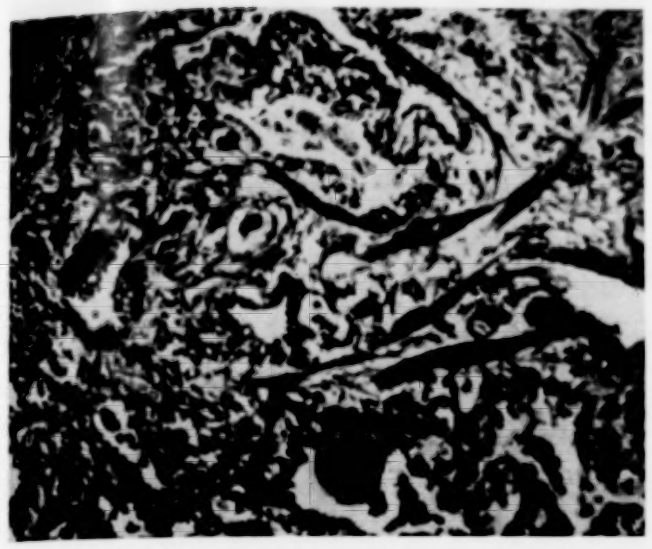


FIG. 6. Irregular strands of smooth muscle traversing the atelectatic parenchyma. No obvious relationship to bronchi. Phosphotungstic acid hematoxylin. × 100.

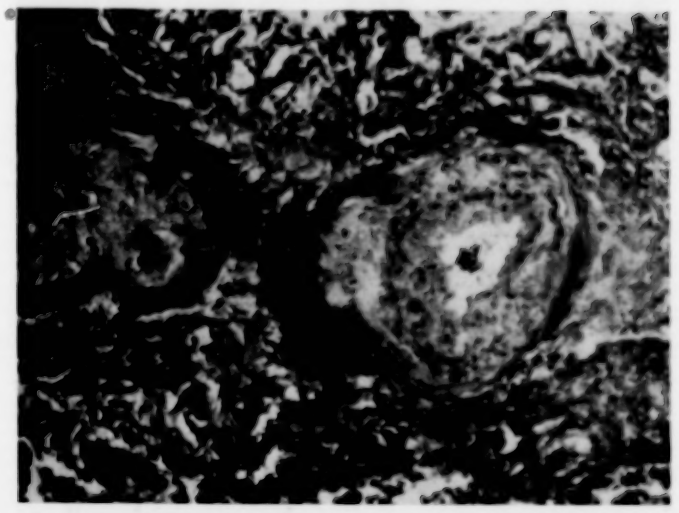


FIG. 8. Medium-sized branches of pulmonary artery showing medial thickening and abundance of smooth muscle in the serosal layer (center of picture). PTAH. × 100.

found near pulmonary or bronchial arteries. Occasionally, the interstitial muscle fibres were continuous with the media. Very occasionally, smooth muscle fibres were seen in the alveolar walls. Areas of alveolar dysplasia consisted of groups of alveoli lined with high cuboidal epithelium and composed of thick mesenchymal tissue. In addition slight interstitial fibrosis was found associated with a moderate infiltration of lymphocytes in the vicinity of bronchi. The bronchial epithelium was intact. No cysts and no areas of emphysema were present.

DISCUSSION

Absence of a pulmonary artery as an isolated abnormality most often involves the right artery (Emanuel & Pattinson, 1956; Schneiderman, 1958; Elder, Brofman, Kohn & Charms, 1958;



FIG. 7. Subpleural network of large vessels probably representing collaterals. Note thick media. PTAH. × 40.

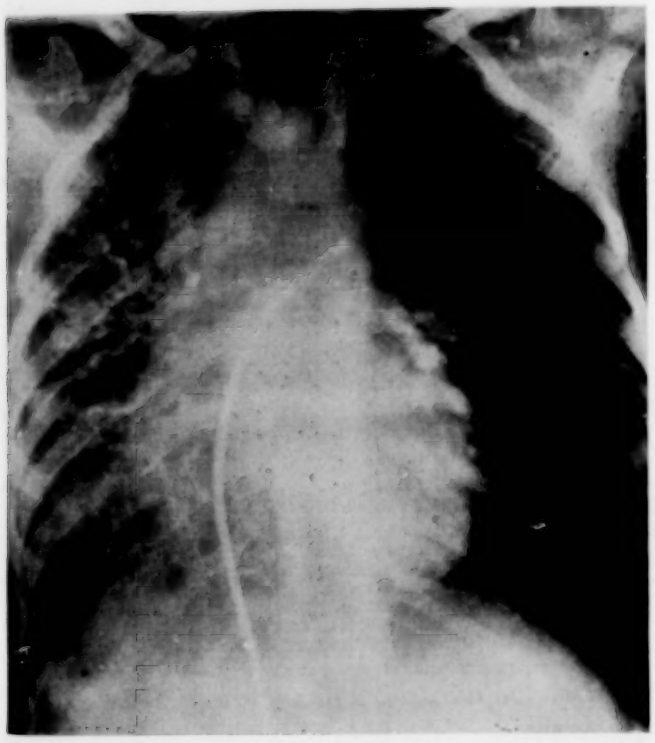


FIG. 5. Filling of numerous small collaterals takes place at the time of vanishing opacification of the aorta.

and slightly enlarged in the left lung. No pulmonary veins were demonstrable in the right lung, neither at this period nor at the time of opacification of the aorta or subsequently. The left atrium, left ventricle and the thoracic aorta were of normal appearance. In the period following maximal filling of the aorta there was a general increase in density over the right lung, apparently due to the filling of numerous small collaterals (Fig. 5). These were seen to extend into the thickened pleural space. The right mammary artery as well as the phrenic artery on the same side were slightly tortuous and wider than their mates. It was felt that branches of the phrenic artery were contributing to the vascularization of the basal portion of the lung. No abnormal vessel was seen to arise from the ascending aorta.

The aforementioned examinations had thus shown hypoplasia with severe stenosis of the right pulmonary artery with a diminished ventilation and no oxygen uptake from the right lung. The working test, showing normal ventilation values during rest and work indicated that the left lung compensated adequately for the absent function of the right pulmonary parenchyma.

Since the right lung was the seat of recurrent bronchopneumonia and did not contribute to oxygen uptake, a right-sided pneumonectomy was performed. During the operation several pleural adhesions were noted; these were highly vascular and bled profusely. There were many dilated and tortuous bronchial arteries in the region of the main bronchus. A thin, almost obliterated pulmonary artery was ligated and cut. The postoperative course was uneventful.

Pathology. The lung was received fixed in formalin. It measured 11 by 8 by 3 cm in its greatest dimensions. It appeared atelectatic and was covered by a 2–4 mm thick fibrous pleura. No definite branches of the pulmonary artery were identified in the hilum. The specimen was firm and without crepitations. On section the colour was grayish white and no air emerged on pressure. The bronchi were grossly normal and three lobes were present.

Histologic examination disclosed atelectasis, abnormal pulmonary and bronchial arteries, areas of alveolar dysplasia, interstitial foci of smooth muscle proliferation (Fig. 6), and a prominent subpleural vascular system interpreted as being collaterals (Fig. 7). All these features, except the myomatosis, have been described in previous reports. The pulmonary arteries showed a thick media, subintimal thickening and narrow lumens (Fig. 8). The bronchial arteries had thick walls with irregular medial hypertrophy. The smooth muscle fibres of the areas of myomatosis were not adjacent to bronchi but were often

right ventricle is directed to only one lung. Results of heart catheterization have shown normal or slightly increased pulmonary artery pressures. Only infrequently has pulmonary hypertension been observed (Anderson *et al.*). The ability of the lung to accommodate to an additional increase in blood flow (for instance at exercise) is, however, limited and may lead to an exaggerated rise in the pulmonary artery pressures on exertion (Elder, Brofman, Kohn & Charms, 1958).

Bronchospirometry performed in our case disclosed that the right lung was responsible for 26 % of the total ventilation. As no oxygen uptake occurred, the ventilation of the affected lung did not serve any apparent functional purpose. The response to exercise was an increase in respiratory frequency but no increase in total ventilation occurred. The deficiency of ventilation had many causes. The atelectasis, the fibrosis and myomatosis, as well as the emphysema of the contralateral lung are of significance.

The roentgenographic features which have been described as typical of the isolated absence of a main branch of the pulmonary artery were present in our case and made it possible to establish a presumptive diagnosis merely on the basis of the roentgen examination. The essential findings were: some reduction in the volume of the affected lung with a consequent shift of the heart and mediastinum towards it, an overdistension of the contralateral lung and a characteristic vascular pattern, suggestive of a collateral arterial supply to the abnormal lung. Similar features may be observed in cases with a markedly stenosed but patent branch of the pulmonary artery (Maier, 1954; Elder *et al.*). Angiocardiography provides the best means of diagnosis (cf. e.g. Steinberg *et al.*; Madoff, Gaensler & Strieder; Maier; Wyman; Flynn, Siebens & Williams; Job, Ilha, Pastons & Campos).

The small remnant of the right pulmonary artery, found in the angiocardiograms in our case, seems to be an unusual finding. A similar case has been reported by Elder *et al.* As the artery was atretic the clinical and roentgenologic features were identical in all other respects to cases in which the pulmonary artery is absent. The left atrium was filled via the pulmonary veins of the left lung. No right-sided pulmonary veins could be detected, not even after the opacification of the aorta had vanished. Narrow pulmonary veins were, however, present in the lung specimen. The failure to demonstrate them at angiocardiography might be due to the markedly reduced circulation to the lung. The collateral arterial vessels in the right lung were opacified after the filling of the aorta but the exact source of this arterial supply could not be established on the angiograms. The widening of the internal mammary and phrenic arteries is, however, highly suggestive of an additional systemic vascular supply other than the bronchial vessels. A detailed study of the collaterals would, however, have required demonstration by thoracic aortography (Anderson *et al.*). Atelectasis, slight fibrosis, myomatosis and the extensive collateral vascular supply, may all account for the increased density of the lung observed roentgenographically. Bronchiectasis in the lung lacking the

Anderson, Char & Adams, 1958; Steinberg, 1958). Eighteen cases are on record, 13 of which involved the right pulmonary artery and only 5 the left. As an isolated anomaly the condition may exist without giving rise to any symptoms. Hemoptyses as well as chronic or recurrent lung infections have, however, been described in a number of patients. Repeated bouts of pneumonia and hemoptyses are generally considered to be indications for pneumonectomy.

Embryologically, the absence of a pulmonary artery is attributed to obliteration of the ventral portion of the pulmonary arch. While Schneiderman put forward the hypothesis of a misplaced pulmonary artery, Anderson *et al.* considered the process as being one of proximal interruption of the pulmonary arch with the primitive pulmonary artery *per se* remaining intact. The primitive artery is connected with the dorsal (ductal) segment of the arch. This segment may be obliterated or persist as a collateral vessel to the lung. The absence of the pulmonary artery will be found on the side opposite the larger of the ductal segments. With a left aortic arch and a left ductus arteriosus, the right main branch will thus be absent. In abnormal hearts with a right aortic arch the reverse will apply.

In our case in which the abnormality also seems to be of congenital origin, the right pulmonary artery was short and narrow. According to the theory of Anderson *et al.*, it seems plausible that the hypoplastic artery corresponds to a portion of the right pulmonary arch. The abnormality thus affords an example of incomplete interruption of the proximal arch with atresia at the hilum. Pulmonary artery branches were found in the lung at histological examination and represent the remaining primitive pulmonary artery. The bronchial vascular system was prominent in the lung and was probably communicating with the pulmonary artery system. It is unfortunate that the specimen was not injected for microangiography or cast-studies that would have disclosed the angioarchitecture of the lung.

The bronchial collateral vessels have been assumed to take part in oxygen uptake in some of the reported cases of absence of the main pulmonary artery (Steinberg, Dotter & Andrus, 1953; Smart & Pattinson, 1956). This has been ascribed to increased partial alveolar tension of the oxygen in the affected lung. In our case, however, no diffusion of oxygen was found. Bloomer, Harrison, Lindskog & Liebow (1949) have demonstrated in dog experiments that one-third of the output of the left ventricle may escape to the bronchial arteries following ligation of a main pulmonary artery when communications between the pulmonary artery and the bronchial arteries have been established. Theoretically, this may lead to an increased load with enlargement of the left ventricle. No such alteration could be demonstrated in our case on the angiocardiogram or at the electrocardiographic examination. This is in agreement with the findings of Loring & Liebow (1954) who have shown experimentally that no significant cardiac hypertrophy follows the functional exclusion of a main pulmonary artery.

When one pulmonary artery is absent or completely stenosed the output of the

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Aberrant Left Pulmonary Artery

ULF RUDHE and PER ZETTERQVIST

In 1938, Scheid (5) described an earlier unknown vascular anomaly tending to lead to respiratory obstruction, namely, *aberrant left pulmonary artery*. The anomaly was detected at autopsy on an infant who had died of suffocation after repeated attacks of apnoea. Since in this case the trachea was also malformed, with inflammatory lesions of its mucosa, it was difficult to assess the importance of the vascular anomaly *per se*. However, during the past five years, 11 cases of aberrant left pulmonary artery without associated malformation of the trachea have been reported (1–4, 6–8). Features common to all the cases were that the bifurcation of the pulmonary artery lay further to the right than normally, and that its left branch did not run, in the usual way, directly to the pulmonary hilum in front of the left main bronchus. Instead, it ran in an arch, first backwards above the proximal part of the right main bronchus, and then to the left *between oesophagus and trachea*. It has been found that, under such conditions, both the lowest part of the trachea and the right main bronchus are apt to become compressed, with resulting respiratory obstruction. Hiller & Maclean (2), who diagnosed three cases, have denoted this anomaly as pulmonary artery ring.

Respiratory difficulties were present already during the neonatal period in at any rate 10 of the 11 cases recently reported, and in all but one a life-threatening condition appeared before two years of age. Stridor has been emphasized as a characteristic feature; in contrast to the conditions in the presence of a vascular ring at the typical site, it was essentially expiratory. The symptoms were exacerbated by respiratory tract infections, and recurrent attacks of dyspnoea and cyanosis occurred. A frequent complication was obstructive emphysema, which was severe in some cases; it was then mainly right-sided, so that physically demonstrable displacement of the mediastinum to the left was present (3, 4, 6). In some cases, roentgenologic examination of the oesophagus indicated interposition of the pulmonary artery between the oesophagus and trachea, and this diagnosis could be confirmed by venous angiocardiography (2).

Death occurred in no less than 8 of the 11 cases. Two children died of cardiac arrest during operation (2, 7), and a third shortly after left-sided thoracotomy, at

pulmonary artery has been found in isolated cases (Steinberg, 1950, 1958; Elder *et al.*, 1958). Anomalies of the bronchial tree have also been observed. The bronchogram and the study of the lung specimen of our case did not reveal any abnormality of the bronchi.

Myomatosis has not been described previously in cases of atresia of the pulmonary artery. In the present case, this feature does not seem to be related to the syndrome of so-called muscular cirrhosis of the lung (e.g., Siebert & Fisher, 1957) as no emphysema or cysts were present. The smooth muscle fibres seemed to be related to the malformed vessels and might represent an uncontrolled overgrowth of vascular components. This hypothesis gains support from our unpublished finding of smooth muscle in alveolar walls in advanced cases of mitral stenosis.

SUMMARY

A case of isolated absence of the right pulmonary artery and myomatosis of the lung is reported. This combination has not previously been described in the literature.

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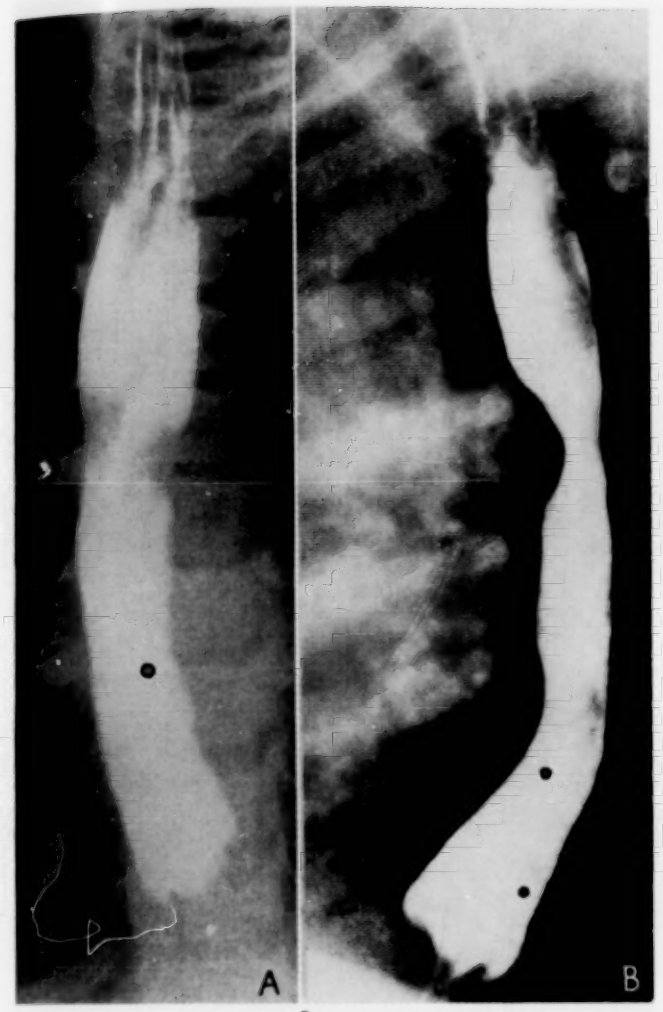


FIG. 1. *A*, frontal view. *B*, lateral view. A transverse impression is seen in the anterior oesophageal wall; it is caused by the left pulmonary artery, which passes between oesophagus and trachea at the bifurcation of the latter. The trachea is slightly displaced forwards. The pulmonary artery runs obliquely downwards and to the left (cf. Fig. 2), as well as somewhat backwards. This explains the slope of the impression and the fact that it is most distinct in the left part of the oesophagus.

with the surrounding tissues, forms a vascular ring around the lower part of the trachea at the origin of the right main bronchus. It was therefore considered warranted to make a detailed analysis of the vascular anatomy.

Selective angiocardiography.—When cardiac catheterization was completed, a no. 7 catheter of Lehman type, with a sealed tip and holes bored in the walls, was introduced into the main trunk of the pulmonary artery. The contrast medium was injected into it through the catheter. The angiocardiograms (Fig. 2) confirmed the assumption that the left pulmonary artery was given off from the right segment of the main trunk, and ran in an arch over the right main bronchus at its origin in the trachea, and then passed to the left hilum between the oesophagus and trachea. The first segment of the left pulmonary artery thus ran parallel to the right, on the upper dorsal aspect of the latter. The branches in the hilum and peripherally had a normal appearance. The pulmonary veins, left atrium, left ventricle, thoracic aorta and systemic arteries showed no abnormal features on the angiocardiograms.

DISCUSSION

Hiller & Maclean (2) have suggested that the anomaly in question is more common than would appear from the few reports in the literature. The observation made in our case, namely, that it does not necessarily cause any obstruction of the respiratory tract, lends support to this assumption.

The diagnostic value of roentgenologic examination of the oesophagus, first pointed out by Wittenborg *et al.* (8), is well illustrated by our case. The aberrant pulmonary artery produces a typical impression in the anterior wall of the oesophagus, a feature best observed in the lateral view. Interposition of the left pulmonary artery is then seen as a local increase in the distance between trachea and oesophagus. The frontal projection shows that the impression in the oesophagus is deepest in its left part, which is explained by the fact that, during its course towards the hilum, the pulmonary artery deviates somewhat in the dorsal direction. A study of the trachea and main bronchi discloses more or less deep compression of the lower part of the trachea, and of the right main bronchus where it takes its origin from the trachea.

which the anomaly was not detected (1). Another child died 11 days after an attempt to decrease the load on the right main bronchus by transplanting the artery and attaching it to the lower trachea (3). Three children with multiple congenital malformations died at a maximum 3 months of age; in these cases, the respiratory obstruction caused by the pulmonary artery anomaly does not seem to have been the only cause of death (1, 8). In one case, the middle and lower lobes of the right lung were removed at 3 weeks of age, owing to severe emphysema with displacement of the mediastinum to the left, but the emphysema progressed in the remaining parts of the lung on both sides, and the patient died of bronchopneumonia at 6 months (6).

One of the surviving patients only had any appreciable symptoms in connexion with respiratory tract infections, and they were then of moderate degree (2). Emergency operation with reconstruction of normal anatomic conditions was performed on the other two patients (2, 4). The clinical results were good in both cases, with only insignificant symptoms after operation, but in one of them postoperative angiocardiography showed occlusion of the left pulmonary artery (2).

Our case, described in the following, differs from all those previously reported in that the anomaly is not associated with any significant symptoms from the respiratory tract. The anomaly was detected as a purely incidental finding at roentgenologic examination of the oesophagus in a child operated on earlier for hiatal hernia.

CASE REPORT

The patient was a boy, born in July 1957. Between 6 and 12 months of age he had repeated respiratory tract infections, with coryza and a cough, as well as anorexia and vomiting. His cough was generally of the "barking" type, as in croup, and slight inspiratory stridor was sometimes heard. Increasing anaemia and blood-streaked vomiting led to detection of hiatal hernia when he was about 1 year old; radical operation with Allison's method was performed in September 1958. The results of operation were on the whole satisfactory, but he returned for a check-up in December.

Physical examination showed a somewhat small but otherwise normally developed 18-month-old boy. Respiration was entirely normal, with no stridor. Heart conditions were completely normal, and the ECG showed nothing pathologic. Cardiac catheterization, performed on the grounds of the unusual roentgenologic finding, disclosed normal conditions of pressure and oxygen saturation in the right side of the heart.

Roentgenologic examination.—The *heart* was of normal size and configuration. *Lungs*: no densities were present. The distribution of the pulmonary vessels was ordinary. Vascularization was normal. The lower part of the *trachea* was slightly displaced to the left and forwards, and a shallow impression was visible at the site of origin of the right main bronchus. The excursions of the diaphragm were normal.

Oesophagus: The sliding hiatal hernia, diagnosed at another hospital, and for which the patient had been admitted to our clinic, seemed to have been completely corrected by operation. The entire oesophagus was slightly dilated, due to an intermittent impediment to emptying in its lower part; this was interpreted as a result of operation. In the anterior wall of the oesophagus, at the level of the carina, a marked indentation was present in the lumen, as well as a local increase in distance from the trachea. The impression in the oesophagus was most distinct in its left part (Fig. 1). No pulsations were visible in this part of the oesophagus, neither at fluoroscopic examination, nor on filming with cineroentgenography. The features were typical of an aberrant left pulmonary artery which, together

aberrant pulmonary artery is situated not only more caudally, at the level of the carina, but also on the anterior aspect of the oesophagus.

Associated anomalies of the circulatory organs or other organs were described in six cases in addition to the first, reported by Scheid (5), in which the trachea was abnormallly narrow, and all its rings except the lowest one were entirely closed. The left pulmonary artery was underdeveloped in one case (2). Other vascular anomalies observed were dextroposition of the aorta with coarctation, aberrant systemic arteries and persistent left superior vena cava (1, 6, 8). Intracardiac malformations were present in two cases, and anomalies of the digestive tract, urinary organs and spinal cord were observed as well (1, 8).

In our case, cardiac catheterization and selective angiocardiography disclosed no anomalies of the heart or great vessels apart from the aberrant left pulmonary artery. The impression made by this vessel in the trachea and right main bronchus was shallow. In view of the fact that the patient had no respiratory tract symptoms that could reasonably be ascribed to the vascular anomaly, no indications were present for correcting it surgically.

SUMMARY

A case is reported of aberrant left pulmonary artery without clinical symptoms, detected at roentgenologic examination of the oesophagus after operation for hiatal hernia. A study of the literature shows that in all earlier known cases this vascular anomaly was associated with symptoms of respiratory obstruction, usually of a life-threatening degree. The value is pointed out of roentgenologic examination of the oesophagus for demonstration of the typical interposition of the aberrant vessel between oesophagus and trachea. In the case in question, this was confirmed by selective angiocardiography, which allowed detailed visualization of the course of the pulmonary artery.

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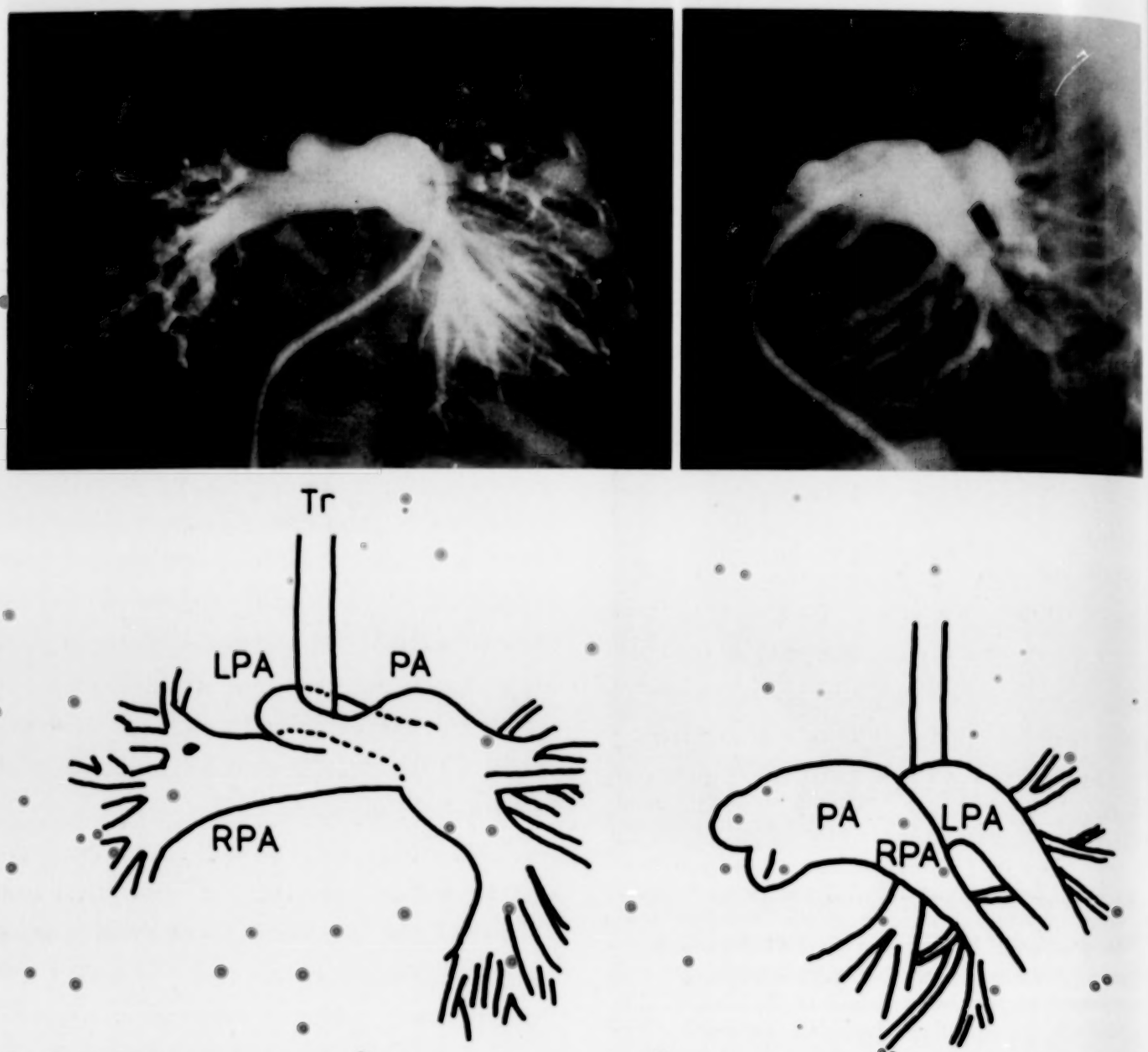


FIG. 2. The pulmonary artery and its branches depicted in the frontal and lateral projections at selective angiocardiography. The left pulmonary artery (cf. schematic drawing) is given off parallel to the right pulmonary artery from the right side of the main trunk. It crosses the right main bronchus at the trachea, and then runs obliquely downwards and to the left to the hilum, where it branches normally. PA, pulmonary artery; LPA and RPA, left and right pulmonary artery; Tr, trachea.

It has been stated that the pulsations of the bulging pulmonary artery appear on opacification of the oesophagus, and that they are thus a direct indication of the presence of a vascular anomaly. In our case, no such pulsations could be observed with certainty. Direct measurements on the angiocardiograms showed that the amplitude of the pulsations amounted to only about 0.5 mm. Presumably, it is scarcely possible to discern such small pulsations in children under 2 years of age without first producing apnoea. From the diagnostic point of view, this seems to be irrelevant, since the impression of the aberrant pulmonary artery in the oesophagus is typical with respect to both shape and position. Thus, it differs from the far more common deformity of the oesophagus produced by the right subclavian artery, when this vessel is given off anomalously as the last branch from the aortic arch, and crosses the oesophagus on its dorsal aspect. The

by Pappenheimer (1955). According to these authors the walls of the glomerular capillaries contain pores of a diameter calculated at about 75 Å. The calculations are based on known data concerning the size of the haemoglobin molecule (Bragg, 1953), which can only pass through the capillary wall in very small quantities.

The high resolving power of the modern electron microscopes, and the extremely refined technique that has been elaborated for their use, have made it possible to observe tissue structures of the size of these pores. Theoretically, therefore, it should be possible to detect whether such pores do or do not exist in the capillary walls. In practice, however, the problem has proved extremely difficult, and no satisfactory solution has been found. I shall give a brief account of my own attempts in this direction and shall at the same time discuss and interpret the observations made by other authors.

MATERIAL AND METHODS

Small portions of renal tissue from different animals under light narcosis were excised, divided into extremely small segments and immediately fixed in isotonic solutions of various heavy metals buffered to pH 7.2. As a rule the fixation was done with the normal 1 % solution of osmium tetroxide, both alone for three hours and in combination with 1 % platinum chloride, barium chloride or uranyl nitrate, first for two hours in osmium solution, then for about one hour in one of the other solutions. Some preparations were fixed solely in solutions of platinum chloride or uranyl nitrate.

After being washed in Tyrode's solution the preparations were embedded in methacrylate in the normal manner (1 part methyl to 19 parts butyl methacrylate) or in Araldite by the method of Glauert & Brieger (1956).

The study also comprised biopsy material from young and healthy human subjects collected by needle biopsy using the technique of Kark & Muerhcke (1954), which was done by Dr. H. Bucht at St. Erik's Hospital. The material was treated by the same methods as the animal tissues.

The specimens were sectioned on a Sjöstrand ultramicrotome or on a Leitz microtome by Fernandez Moran. They were studied in an electron microscope RCA model 2*d* equipped with condenser aperture and objective aperture of diameter 0.010 in. and 0.030 in. respectively.

RESULTS

The structure of the glomerular capillaries of different animals, using osmium fixation, has been described by numerous authors. (References in Bergstrand, 1957.) The material on which this discussion is based has been partly described earlier, that relating to experimental animals by Bergstrand (1957) and to human subjects by Bergstrand & Bucht (1958).

The wall of the glomerular capillary consists of an inner, very thin layer of endothelium, a basement membrane, and an outer covering cell, usually called the epithelial cell (Fig. 1). Within the greater part of the capillary wall the endothelial cell is very thin and consists of the cell membranes with a

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The Morphological Basis for the Filtration Process in the Glomeruli

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Ever since Cushny (1926) presented the first clear formulation of the theory that urine is formed by filtration through the glomerular capillary walls and Richards (1938) presented the first experimental proofs of the correctness of this theory, it has been an intriguing problem for all morphologists engaged on the anatomy and pathology of the kidneys to investigate the structures which render the filtration process possible.

Urine formation in the kidneys is an altogether specific process. In principle, however, there is no difference between the filtration through the walls of the glomerular capillaries and the transfer of fluid through the capillary walls in other organs, for example the striated muscles. Glomerular filtration is easily measurable under either physiological or pathological conditions by clearance tests, which are so well known as to require no mention in this context. The passage of fluid through other capillaries has been studied by means of numerous physiological tests, especially through perfusion of the extremities in living animals. Another method is to study the passage of fluid through artificial membranes of, for example, collodion. Such membranes are easy to make and their properties can be varied so as to equate their permeability with that of the blood capillaries.

Our understanding of the nature of the filtration process is based on the abundant data collected by these various methods. It is generally considered that the capillary walls contain very fine pores which pass fluid and molecules dissolved in it up to a certain size, while larger molecules, colloids and cellular elements are under normal conditions retained in the blood stream. Accordingly the *composition* of the filtrate is determined primarily by the diameter of these pores, while its *maximum quantity* is determined by the number of pores per unit of area of capillary wall. The quantity of the filtrate is determined, in other respects, essentially by the pressure gradient through the capillary wall from the blood to the intercellular space and by the thickness of the capillary wall.

Detailed accounts of these problems, especially in relation to the glomerular filtration, have been given by Pappenheimer, Renkin & Borrero (1951) and

Other researchers express a contrary view, to the effect that the basement membrane consists of three separate layers as first described by Rhodin (1955). There appears to be full concurrence at all events that no fibrils or pores can be positively detected in the basement membrane after fixation in osmium. The epithelial cell has profuse ramifications with a multitude of fine protoplasmic processes which fasten one beside the other on the outer aspect of the basement membrane. Between these foot processes or pedicles there are narrow slits.

Fixation with other heavy metals than osmium shows up the epithelial and endothelial cells very much less clearly, while failing to reveal any distinct structure in the basement membrane. Fixation with osmium followed by platinum or uranium may often give a better reproduction of the cell membranes, as also happens when using the combination of osmium with phospho-tungsten acid (PTA). No additional structure becomes apparent in the basement membrane. Barium chloride has been used to produce a compound between the barium metal and free sulphate groups which should be present in the large molecules of glucoproteins, which are probably the most important component in the basement membrane. But this method as well has failed to reveal any structure in the basement membrane of healthy animal or human subjects. In diabetic patients I have found a distinctly lamellar structure in the hyaline masses which precipitate on the basement membrane (Bergstrand & Bucht, 1959), but from this observation it is scarcely possible to draw any conclusion concerning the structure or functional role of the basement membrane under normal conditions.

DISCUSSION

One thing appears to be clear, and that is that the structure of the glomerular capillaries must favour the rapid passage of large quantities of fluid. Pappenheimer shows that the filtration through the glomerular capillaries is as much as 100 times greater than through other capillaries. Opinions differ, however, on the role in filtration played by the different structures of the glomerular capillary.

Vincent Hall (1957) was, like myself, unable to discern any structure in the basement membrane and therefore considered it to be a gel without specific properties of permeability. The pores must be sought elsewhere. The fenestrations in the cytoplasm of the endothelial cell are, of course, far too large. They have an important role, on the other hand, in providing a free passage for the blood to large areas of the basement membrane. The spaces between the processes of the epithelial cells, too, are generally of such size as to be unthinkable as filtration pores. According to Hall this is due to shrinkage of the epithelial cells during fixation, which considerably increases the spaces between the processes. By measurements on rat preparations fixed with the utmost care, Hall considered he could determine the distances between the processes of epithelial cells as 100 Å. He claims accordingly that these spaces, the so-

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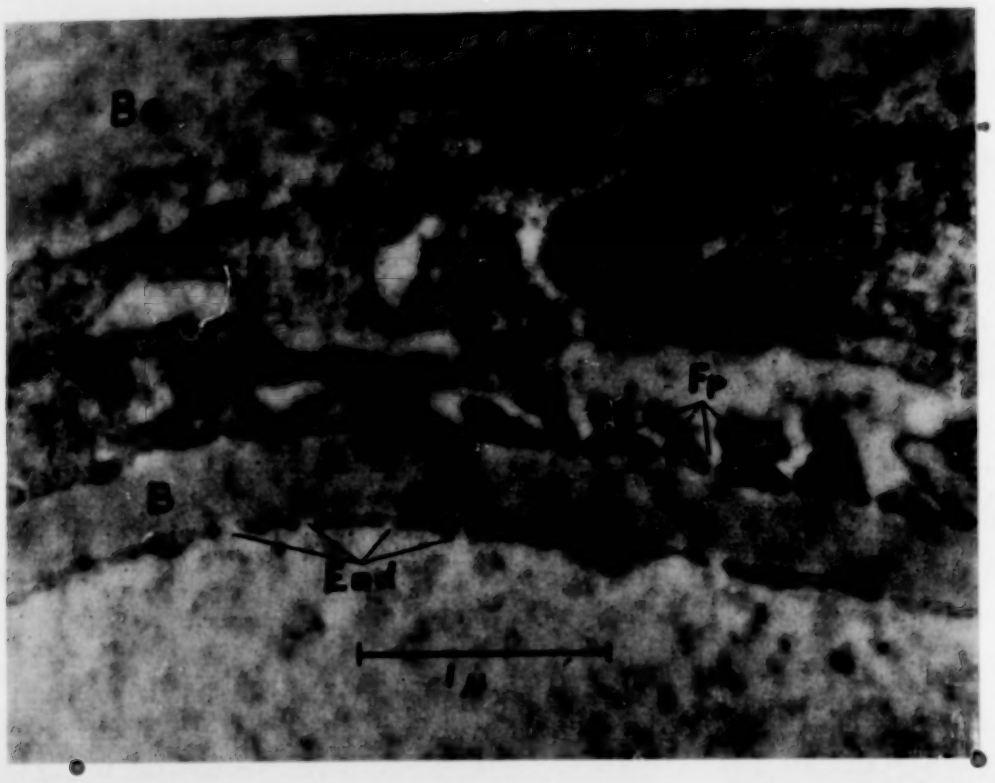


FIG. 1. Rat. Fixation: osmium tetroxide. Embedment: Araldite. Transverse section of capillary wall. Endothelial cell (*End*) with fenestrations in cytoplasm. Basement membrane (*B*) of the capillary. Epithelial cell (*Ep*). Basement mem- in Bowman's capsule (*Bc*). Filtration slit pores (*Fp*) according to Hall.

very minute layer of cytoplasm between them. In the endothelial cell there are round or oval spaces of a diameter which may be 300 Å or above. The basement membrane forms a homogeneous layer between the endothelial and epithelial cells (Fig. 2). Owing to shrinkage of the specimen during preparation a narrow paler zone is often seen adjoining the endothelial and epithelial cells. In my definite opinion, however, this is always an artefact.

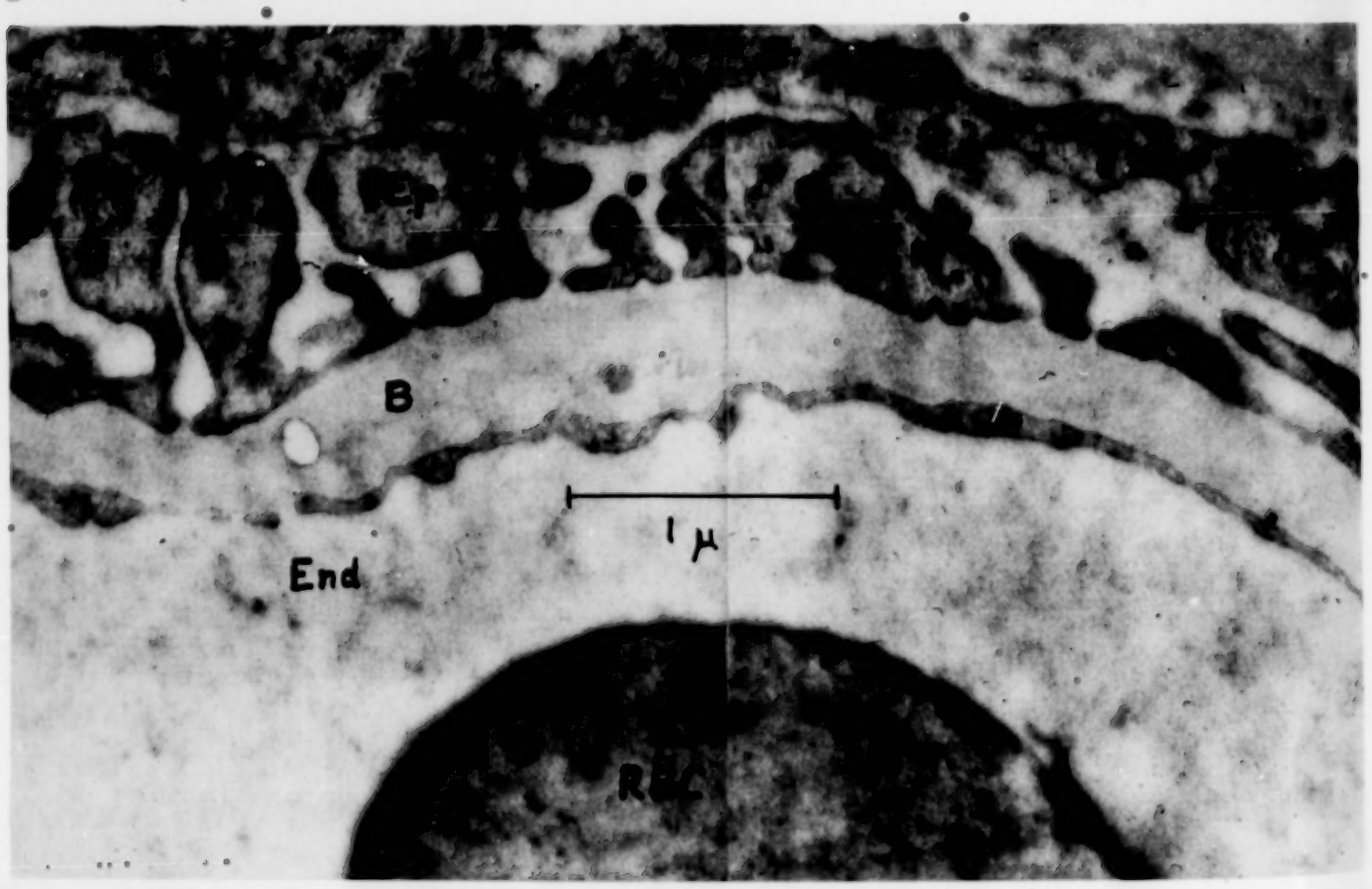


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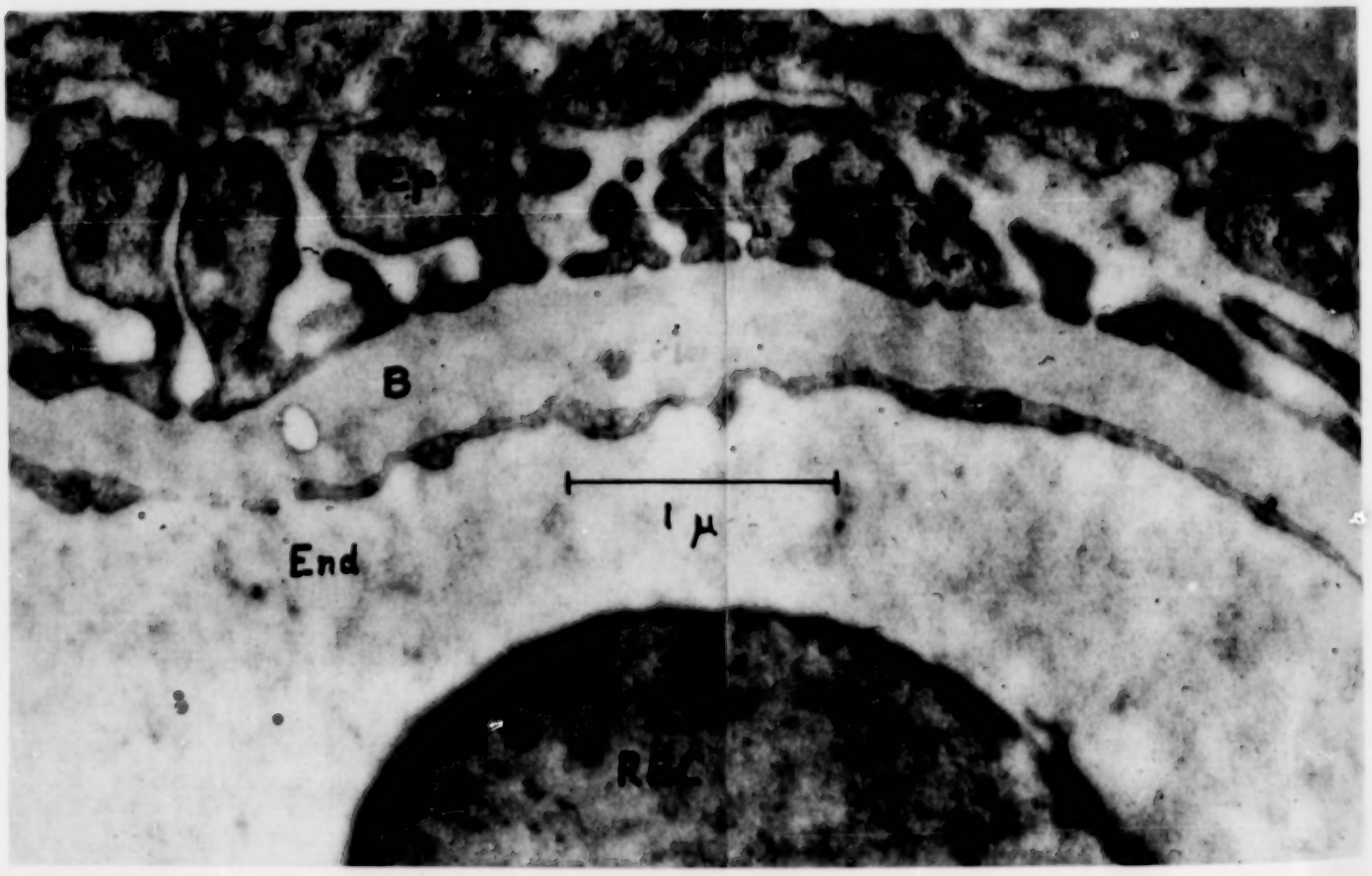


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renal changes in human subjects with disturbed filtration are, in my opinion, still too scanty to justify any positive conclusion regarding the morphological cause of the functional disturbance. There is a strong indication, however, that the changes are localized to the basement membrane, which in turn suggests that the structures which constitute the morphological basis for filtration should also be sought in that quarter.

Hall's assumptions also imply that the epithelial cell processes are under normal conditions very stable structures of definite form. Investigations made on material from healthy human subjects seem to indicate, however, that this is by no means the case, at least not in man. Thus considerable variations in the appearance of the epithelial cells are found in different sections of the same glomerulus. Nor is it unusual to find great variations even within different sections of the same epithelial cell, with large or small vacuoles in varying numbers in the cytoplasm and with various forms of mitochondria. Large or small electron-dense granules are frequently observed, similar to those in the tubular epithelium in, for example, protein resorption (Bergstrand & Bucht, 1959). These observations suggest a very high metabolic activity in the epithelial cells, probably a resorption of water and dissolved substances in varying quantities and proportions. In my opinion it is extremely difficult to imagine that under such conditions the processes of the epithelial cells can be fixed structures with constant spacing between them. Observations from man suggest, on the contrary, that they are very variable and may change both in size and shape within wide limits without causing functional disturbances. It is improbable, therefore, that they play the role assumed by Hall in the filtration process in man.

This is not to say, of course, that they have no significance for filtration. In my opinion the spaces in the cytoplasm of the endothelial cells and between the epithelial cell processes cooperate in such a manner that a free passage is afforded for the blood to the basement membrane and for the filtrate from the latter, within a limited area which determines the maximum volume of the filtrate. The filtration pores, on the other hand, which determine the composition of the filtrate, must be sought in the basement membrane. The reason why we have thus far not been able to demonstrate their existence is that the mucopolysaccharides, which are probably the essential component in the basement membrane, have so little affinity for osmium or other heavy metals that, by the methods employed hitherto, we cannot reproduce the finest details even though they are within the resolving power of the electron microscope.

The question of the morphological basis for the filtration process in the glomeruli can accordingly not be said to have found a solution. The theory put forward by Hall can, in my opinion, not be the correct interpretation. His theory is nevertheless of considerable importance since it is the first attempt to correlate the morphological observations in the electron microscope with the results of physiological examinations. The problem has hereby been stated pre-

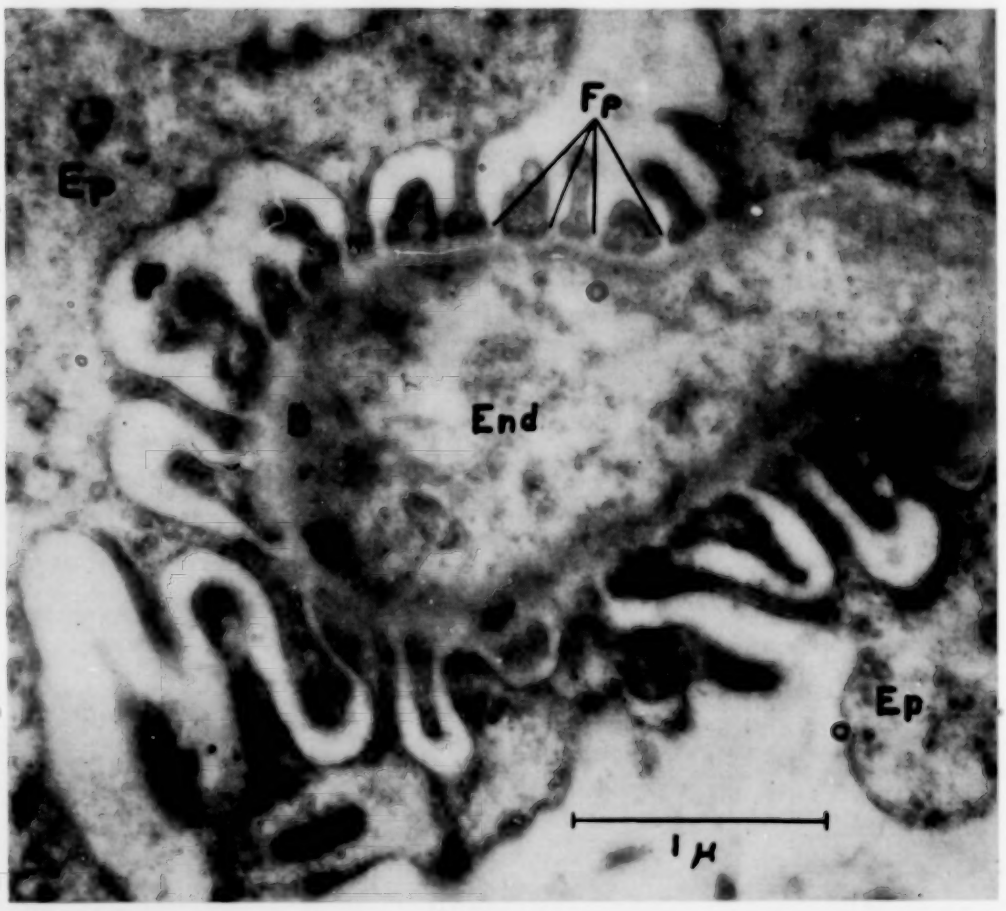


FIG. 3. Rat. Fixation: osmium tetroxide + barium chloride. Embedment: methacrylate. Oblique section of capillary. Filtration slit pores (*Fp*) appear most clearly in this form of section. Cf. Figs. 1 and 2.

called filtration slit pores, constitute the actual morphological basis for the filtration (Fig. 3). It is their diameter which determines the composition of the filtrate and their number which determines the maximum quantity of the filtrate. In further support of this assumption Hall maintains that, in patients with renal diseases accompanied by proteinuria and lowering of filtration —e.g. glomerulonephritis or lipoid nephrosis (Vernier, Farquhar, Brunson & Good, 1956; Farquhar, Vernier & Good, 1957) or in experimental glomerulonephritis (Hall & Heymann, 1957; Miller & Bohle, 1957)—the epithelial cells become destroyed early in the course of the disease, with confluence of the cell processes, so that the spaces between them are largely eliminated.

Substantial objections may, however, be raised against these assumptions. According to Hall the filtration slit pores are 100 Å in diameter, while Pappenheimer calculates the pores in the capillary walls to be about 75 Å. The difference may appear slight in view of the great difficulty of making exact measurements and of the minute dimensions involved, but in reality is highly significant.

Experience from the study of other renal diseases, such as diabetic glomerulosis, in patients with a clearly lowered filtration fraction—that is, with a definite obstruction to the filtration process—suggests that the most important cause in these cases has been a thickening and change of the basement membrane in the capillary walls (Bergstrand & Bucht, 1959). A scrutiny of the material presented by Vernier, Farquhar, Brunson & Good (1956) shows, too, that there has been no proven diminishment of glomerular filtration, at least not in lipoid nephrosis. Investigations of the

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Osteochondroma in the Posterior Mediastinum

Report of a Case, with a Review of the Literature

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Osteochondroma in the mediastinum is a rare condition. In such cases the vertebral column, the ribs or the sternum may serve as a starting point for the tumour. The tumour may originate from practically any bone preformed in cartilage and is particularly common near the ends of the long limb bones. It occurs in a solitary and an hereditary multiple form. Geschickter & Copeland (1949) reported 291 cases of the former and 27 cases of the latter. Of this total of 318 cases of osteochondroma the thoracic skeleton was involved in only three—one case each of costal, sternal and vertebral localization. Meyerding (1927) reported 265 osteochondromas in 232 patients. Five of the tumours were localized in the thoracic skeleton, in each instance in the ribs. It is not known whether the growth extended into the mediastinal region in any of these cases. The vertebral column seldom seems to be the seat of osteochondroma. In the series of Geschickter & Copeland (1949) mentioned above the vertebral column was involved in 13 cases. Apart from the case with thoracic localization the cervical region was involved in one case and the lumbar region in 9 cases. For the remaining 2 cases the localization was not stated. In Meyerding's material there was only one case of osteochondroma in the vertebral column, and that was in the lumbar region.

The tumour is built up of bone and cartilage, and is covered by a periostal layer. Histologically it is benign and resembles the endochondral ossification. The risk of malignancy, with secondary development of chondrosarcoma, is small, probably not exceeding 1–2 % (Lichtenstein, 1952). O'Neal & Ackerman (1951) point out that there is a tendency to underdiagnose cartilage tissue tumours and associate themselves with Lichtenstein's criteria for the histological evaluation of the malignancy of these tumours.

As a rule, the clinical picture presents few symptoms. As the tumour grows in size, however, it may gradually produce pressure symptoms from surrounding tissues and organs. The localization of the tumour is then, of course, of decisive importance for the symptom picture,

cisely and discussion has been aroused. It is to be hoped that coming investigations will yield additional results which bring the question closer to its solution.

SUMMARY

A brief account is given of the facts known hitherto concerning the structure of the glomerular capillaries as it appears in the electron microscope. Hall's theory, based on known physiological data and anatomical observations, concerning the morphological basis for the filtration process in the glomeruli is briefly reviewed. The present studies of, especially, human kidneys have produced results which are at variance with Hall's theory. It is here claimed that, in the basement membranes of the capillaries, there are in all probability fine pores the diameter of which has been calculated by Pappenheimer to be 75 Å, and that it is these pores which determine the composition of the filtrate.

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peared: shortness of breath, pains along the left costal arch, feeling of pressure in the chest. Until then the patient had been able to work, at times on very hard manual labour, but once the symptoms appeared they progressed rapidly. The patient was admitted to the Karolinska Sjukhuset on Aug. 28, 1958, in a very low condition, with dyspnoea at rest of inspiratory type and with retractions and palpitation upon moderate exertion.

The physical examination revealed nothing exceptional apart from tracheal stridor. Blood pressure 130/100. Completely normal laboratory values, SR 2–6 mm. X-ray at admission showed a large tumour 16 × 15 × 12 cm in the posterior mediastinum at the level of the middle thoracic vertebrae. It was polycyclic, well defined, and irregularly calcified. The structure of the 6–7th vertebrae was affected, the 6th rib was eroded on its lower edge within an area 7–8 cm long, and the 6th and 7th ribs were bent apart (see Figs. 4–6). The trachea and oesophagus were displaced forwards. Close to the tumour there was a small compression atelectasis within the adjacent lung lobe. Progression continued after admission: signs of congestion in the upper half of the body and further deterioration of the respiratory function made operative measures urgent.

On Sept. 8, 1958, left thoracotomy was performed. There was found a fixed tumour in the posterior mediastinum; this was displacing the lung and blood vessels forward and was growing around the aorta. The freeing of the aorta was made difficult by the fact that the intercostal arteries were also encircled by tumour tissue and difficult to

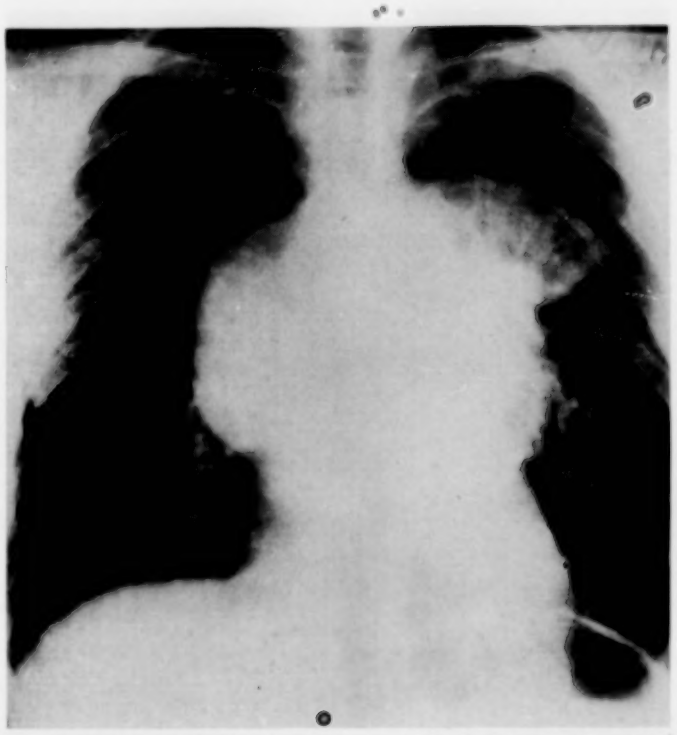


FIG. 4. X-ray picture from August 1958; frontal view.

identify. During the dissection there was haemorrhage from the posterior of the aorta in the upper part of the tumour, followed by a fall in blood pressure and ventricular fibrillation. After heart massage and replacement of the blood loss the heart was defibrillated, and the



FIG. 5. X-ray picture from August 1958; lateral view.

which in unfavourable circumstances may be very alarming. This is illustrated by the following case of an osteochondroma which expanded in the posterior mediastinum.

CASE REPORT

A 35-year-old man admitted to the Clinic of Thoracic Surgery at the Karolinska Sjukhuset for an intrathoracic tumour.

Parents and 7 siblings healthy. The patient himself had always previously been in good health. A symptomless tumour was discovered by mass radiography in October 1954. Afterwards the patient was admitted to a county hospital for further examination. The X-ray photographs confirmed the previous finding. Bronchoscopy was negative.

At the next routine X-ray examination in 1956 the tumour was found to be somewhat larger than earlier. In June 1958 the first subjective symptoms ap-

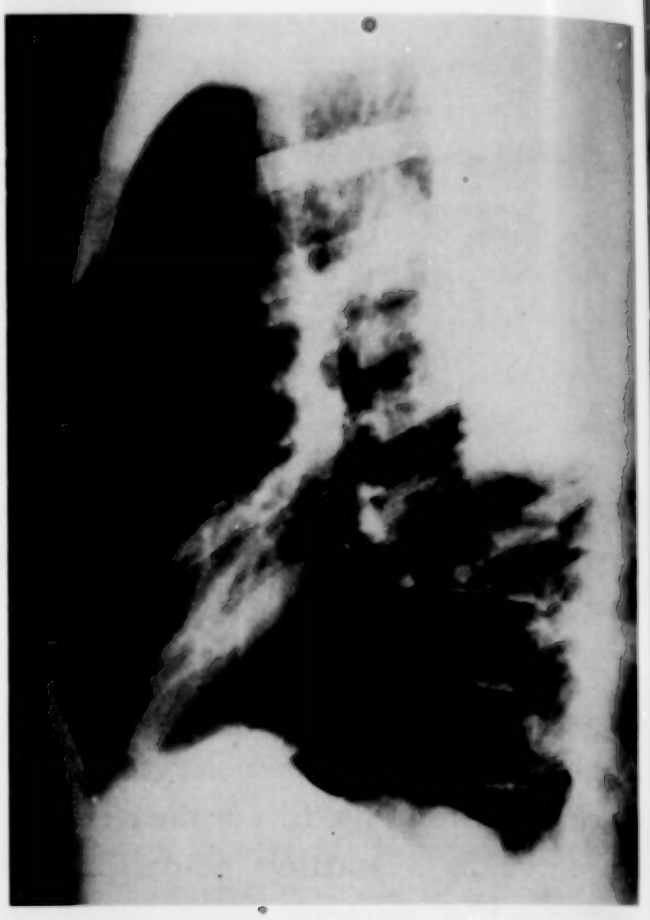


FIG. 2. X-ray picture from January 1955; lateral view.

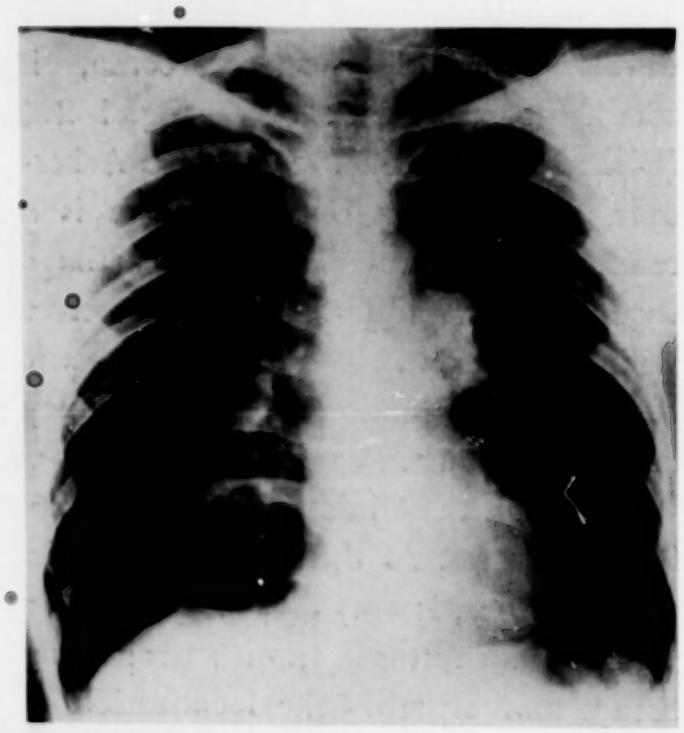


FIG. 1. X-ray picture from January 1955; frontal view.

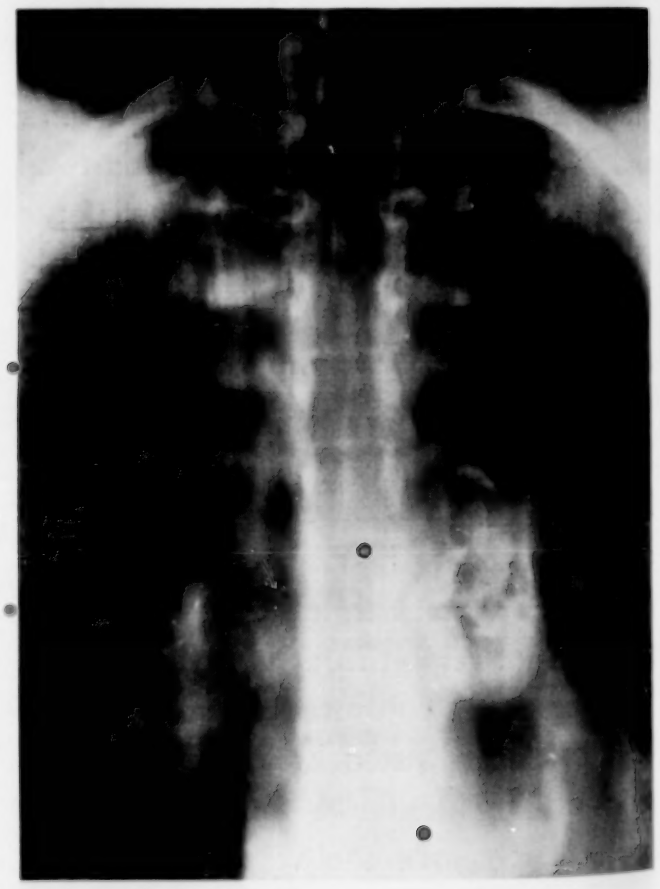


FIG. 3. X-ray picture from January 1955; tomogram.

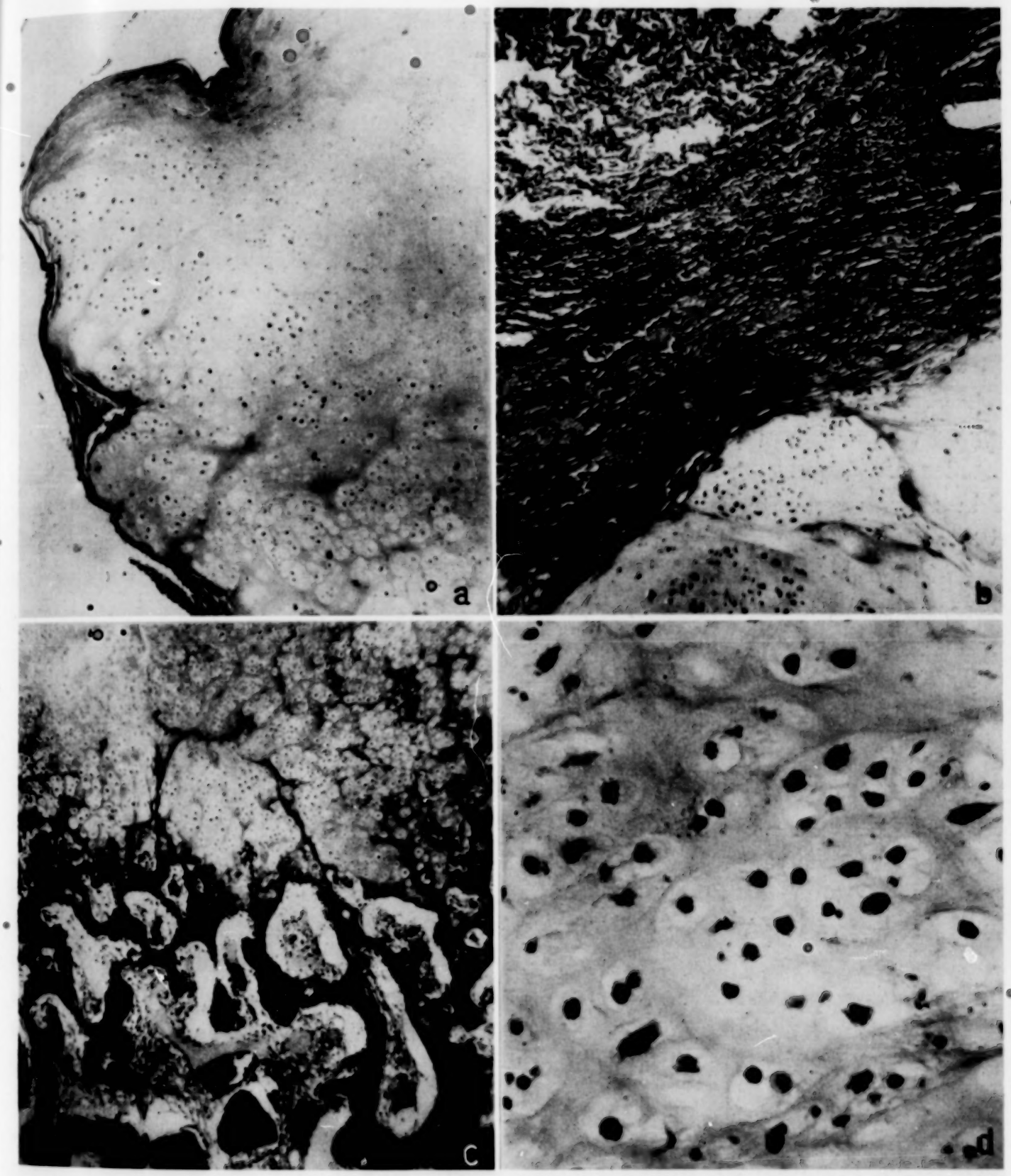


FIG. 7. Microphotograph of various parts of the osteochondroma (van Gieson staining). (*a*) General picture of the periphery of the tumour, showing the lobular cartilage tissue formations and the fibrous capsule (× 75). (*b*) Section from the dorso-medial part of the right lung, showing the thick, fibrous capsule which separates the tumour (below, right) from the atelectic lung parenchyma (above, left) (× 75). (*c*) The endochondral ossification zone with bony trabeculae and marrow spaces (below) and lobularly growing cartilage (above); (× 75). (*d*) Detailed picture of an area of more proliferative character with a certain nuclear polymorphism. Note a double nuclear cell (below, left); (× 480).

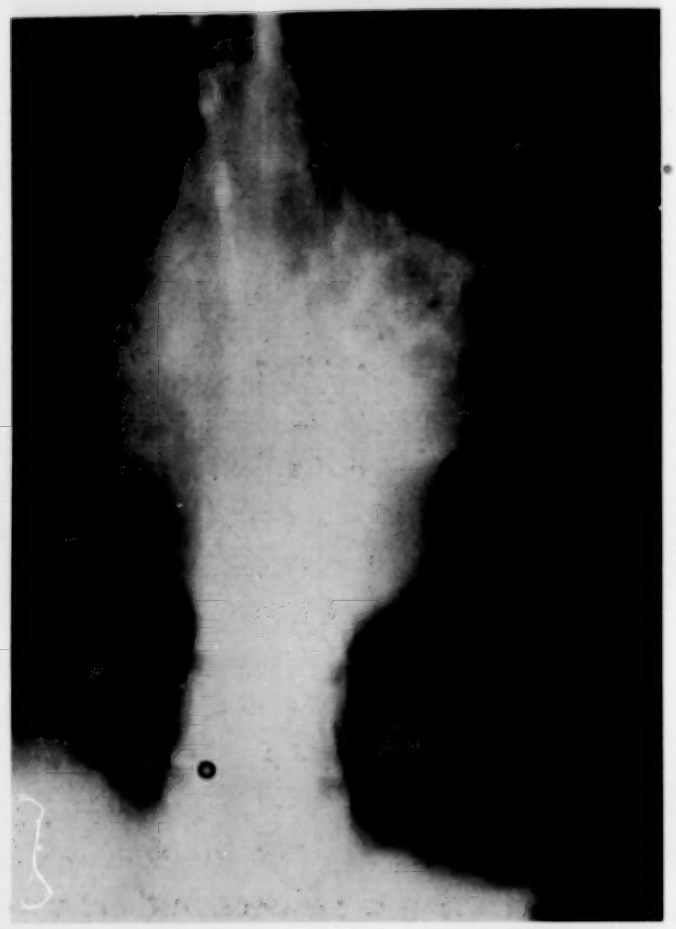


FIG. 6. X-ray picture from August 1958; tomogram.

damage in the aorta wall was repaired. The mode of growth of the tumour rendered it inoperable. It was also bleeding profusely from the spongiosa-like resection surface. As a palliative measure the part of the tumour which was compressing the trachea was removed subcapsularly, after which the resection surface was coated with gel-foam. Immediately after the operation the patient's blood pressure was maintained and tracheotomy was performed. As it was noticed that the flow of blood from the drainage tubes was increasing it was decided to reoperate. The blood loss, however, amounted to 500 cc in the final 15 minutes and the patient died before reoperation could be started.

PATHOLOGY

The specimens obtained at operation consisted of a number of pieces of tissue up to fist size of a brown-red-whitish colour and irregularly lobulated. Consistency was firm to bony. Microscopic pictures agreed with those of the post-mortem findings.

Post-mortem findings: There was found to exist a bilateral haemothorax with 750 cc blood in the right pleural cavity and 850 cc in the left. In the posterior mediastinum there was encountered a whitish-grey, cartilage-hard, well-defined and somewhat lobulated tumour in an operatively changed, haemorrhagically imbibed area. Along the left side of the vertebral column, from the level of Th 5 to Th 7 there was a mass of tumour tissue, which partly filled the sulcus costovertebralis posteriorly and reached anteriorly to a plane a few centimetres ventrally of the vertebral column. On the left the tumour ended abruptly with a haemorrhagically discoloured resection surface, cartilage- to bone-hard and in parts disintegrating. On the ventral side of the vertebral column the tumour mass changed over to the right in a tumour lobe of the size of a newborn's head, protruding into the right pleural cavity. Here there were a number of loose adhesions to the dorso-medial portion of the right lung. Whereas in other respects the tumour was sharply defined and entirely free of the surrounding tissues, posteriorly it was firmly attached to the vertebral column at the height of Th 6–7. The tumour was growing in a claw-like manner around these vertebral bodies, whose breadth

be closed on both sides of the resection with the patient showing only short signs of congestion after the operation. Herlitzka & Gale (1958) reported two cases of osteochondroma in the posterior mediastinum, not described in detail. The first was a man, 26 years of age, who was operated on after symptoms lasting 4 months; at the operation a tumour 10×7 cm was removed; the second case was a 54-year-old woman from whom a symptom-free tumour was removed after having increased in size during an observation period of two years.

These cases, of which the one in the present study ended in the patient's death, support earlier definite warnings against delay in cases of mediastinal tumours (Heuer & Andrus; Blades; Burnett, Rosemund & Bucher, 1952; Kunkel, 1956; Nelson, 1957; Herlitzka & Gale; Streete & Thomas, 1958). The mediastinum, with its wealth of organs, is the seat of tumours of many different kinds; thus Sabiston & Scott (1952) reported 101 cases of 26 forms of mediastinal tumours. As a result, the risk of malignancy is particularly difficult to assess; in large series it is stated to be between $\frac{1}{3}$ and $\frac{1}{4}$ (Burnett *et al.*; Ringertz & Lidholm, 1956; Herlitzka *et al.*; Streete & Thomas). X-ray examination reveals most mediastinal tumours (Ringertz & Lidholm) and at the same time also shows the localization—a valuable aid to a probability diagnosis, as the most common tumours have typical predilection positions (Brewer & Dolley, 1949; Kunkel; Herlitzka *et al.*). As Maier (1953) and Freour & Serise (1958) have pointed out, there are also clinical signs of importance, but X-ray is the most valuable kind of isolated investigation, possibly supplemented with special examinations to secure the diagnosis of mediastinal tumour. As soon as this has been established, operative measures should not be delayed by unnecessary further examination (Sabiston & Scott), for the diagnosis depends on the study of specimens obtained at operation.

Even the benign tumours are clear cases for operation; with time they grow, producing pressure symptoms and involving great risks for their removal by operation. According to Maier there are only two contra-indications against operation in the case of mediastinal tumours: (1) the tumour is secondary or has metastasized; (2) the patient's condition makes operation inadvisable.

SUMMARY

Osteochondroma in the mediastinum is rare, according to large series in the literature.

A 35-year-old man with this disease was operated on, on vital indication, but died when the tumour proved technically inoperable in spite of its histologically benign character.

Previously published similar cases are reviewed.

The importance of broad indications for operation of mediastinal tumours is emphasized and receives further support from previous studies.

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was considerably reduced, and partly filled the sulcus costo-vertebralis on both sides. Nowhere were there found changes indicating tumour metastasis. The weight of the heart was 330 g and there was a slight hypertrophy of the left ventricular wall. No arteriosclerotic changes. The sutures in the aorta wall left no gap. Further gross pathology of no interest.

Histological study revealed a benign tumour of osteochondromatous character (see Fig. 7). Thus the tumour was built up in its peripheral parts of irregular lobular cartilage tissue formations with thin fibrous septa interlobularly. The cells as a rule were rather thinly spread and of monomorphous character. There were, however, isolated areas of a more proliferative appearance with greater cellularity and slight nuclear polymorphism in the form of some isolated cells with a somewhat larger or double nucleus. In the more central parts of the tumour was observed much endochondral ossification with marrow spaces containing fatty bone marrow, in places rather rich in blood-filled vessels, though without angiomatous features. The tumour was surrounded by a thick, fibrous capsule and nowhere showed any sign of infiltrative growth. The adjacent lung parenchyma was compressed and atelectatic. Further histological examinations supported the diagnosis of shock with congested and, in places, massively haemorrhagic and atelectatic lung parenchyma.

Diagnoses: Osteochondroma in the posterior mediastinum, postoperative; bilateral haemothorax; congestion, haemorrhages and atelectasis of lungs; hypertrophy of left ventricular wall, slight.

DISCUSSION

The frequency of osteochondroma among mediastinal tumours is difficult to assess, as several surveys of mediastinal tumours exclude those which take their origin from the thoragic cage in spite of the fact that they are clinically similar. Heuer & Andrus (1940) pointed out that chondroma is unusual in the mediastinum and could find in the literature only 14 cartilaginous tumours, including malignant ones. They mentioned a case published by Graham in 1935: a chondroma which started from the vertebral column and was growing in the posterior mediastinum. Blades (1946) mentioned among miscellaneous tumours in the mediastinum an osteochondroma, which, however, was not described in detail. Ilgenfritz (1951) reported the case of a middle-aged man with a swelling on the left-hand side of the neck, which for 13 years had passed under the diagnosis of goitre and had been treated with iodine. He was operated on, and behind the normal thyroid gland there was a hard tumour; biopsy showed osteochondroma. On reoperation it was possible to resect the tumour which measured $12 \times 4 \times 6.5$ cm, but its pressure on the common carotid and subclavian arteries had led to partly irreparable brain damage. Lüdeke (1957) described a man with a chondroma in the upper mediastinum, not further specified, which had been diagnosed 7 years before and which finally compressed the superior vena cava from the rear. On operation it was found necessary to divide this vein, which, owing to a well-developed azygos system could

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Arterial Spasm Treated with Sodium Acetrizoate

PERCY LINDGREN, BJÖRN NORDENSTRÖM and GUNNAR TÖRNELL

Roentgen contrast medium has been used earlier in certain cases for therapeutic purposes. Demel & Sgalitzer (1937) and Klein (1937) noted a favourable effect in peripheral circulatory disturbances after arteriography with iodopyracet (Perabrodil). The former authors observed by chance that marked improvement took place in immediate association with arteriography in a case of Raynaud's gangrene. They therefore started to use iodopyracet in the treatment of other patients with peripheral circulatory insufficiency. Distinct improvement was seen in a number of cases. The warmth of the extremities increased, and the pain disappeared. The improvement often persisted for some time after treatment. Its effects were ascribed to the vasodilator properties of the contrast medium in question.

Klein also treated patients with peripheral circulatory insufficiency in this way. The examinations were performed systematically, with repeated intra-arterial injections of Perabrodil and Uroselektan. The capillary circulation was also studied (Klein & Spiegel, 1936). In a first phase, immediately after injection, vasodilatation was maximal, with marked hyperemia and an increase in the number of open capillaries. This was accompanied by a decrease in oxygen diffusion in the tissues, and a rise in the oxygen content of the venous blood. In a second phase, the oxygen uptake increased in the tissues. The arteriovenous oxygen difference then rose to considerably in excess of normal. With large doses of contrast medium, this phase occurred after 10–20 minutes, and with small doses after 3–5 minutes. Klein stated that many of the patients had been distinctly improved by this treatment. This field of application of Perabrodil and Uroselektan has, however, practically fallen into oblivion.

Since the vasodilator effect of sodium acetrizoate is considerably greater than that of iodopyracet, it was considered of interest to test it as a therapeutic medium in peripheral circulatory disturbances. Sodium acetrizoate (Acétiodone, Diaginol, Rheopak, Triurol, Urokon) is a roentgen contrast medium that has been used since about 1950 for, e.g. angiography. Its importance as contrast medium has, however, been reduced after the introduction of others of the diatrizoate type (Hypaque, Renografin, Uro-

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still no pulsations. Ten ml of 70 % sodium acetrizoate (Rheopak, Astra, Sweden) were then injected into the proximal part of the brachial artery through a narrow catheter. This produced violent pain, but the blood immediately started to pulsate strongly through the vessel. The incision in it was resutured, and good circulation was then present in the forearm and hand. No circulatory disturbances could subsequently be observed in the arm.

Case 2.—A 23-year-old woman with aortic stenosis combined with aortic incompetence. A no. 10 single-lumen catheter was inserted into the right radial artery under local anesthesia (lidocaine without addition of a vasoconstrictor). During the manipulations, the brachial artery contracted, so that the catheter could be withdrawn from the vessel only with difficulty. Ten ml of 70 % sodium acetrizoate (Rheopak) were injected into the axillary artery via a narrow catheter. Injection produced fairly great, immediate pain in the arm. The original catheter was reintroduced, and catheterization could then be performed without any difficulty. No spasm occurred in the vessel during the rest of the examination.

Case 3.—A 30-year-old woman with a cyst of the right lung. It was intended to introduce a double-lumen catheter with balloon into the thoracic aorta via the left radial artery. The radial and ulnar arteries were exposed under local anesthesia (lidocaine without addition of a vasoconstrictor). Both vessels were fairly slender, and the catheter could not be introduced into either of them. An attempt was then made to dilate the ulnar artery with the help of sodium acetrizoate. A thin plastic catheter was introduced through the incision into the lower part of the brachial artery, where 10 ml of 70 % sodium acetrizoate (Rheopak) were injected. The patient felt intense but brief pain. The arteries dilated immediately; the balloon catheter could then be introduced through the vessel, and the examination carried out as planned. No complications occurred in connexion with it.

OBSERVATIONS ON CATS

The blood flow in the femoral vein was recorded with a similar method to that described earlier (Lindgren & Törnell). A local increase in vascular tone was produced both by electric stimulation of the abdominal sympathetic chain, and by intra-arterial infusion of noradrenaline.

In the anesthetized cat, normal vascular tone is usually maintained with an impulse frequency in vasoconstrictor nerves of 1–2 per second (Folkow, 1952), whereas 6–8 per second are stated to give almost maximal vasoconstriction. In our experiments, stimulation took place with 10 impulses per second, which produced marked vasoconstriction with a great reduction in the blood flow.

A typical experiment is shown in Fig. 1. During vasoconstriction—the blood flow was reduced from 3.5 ml/min. to 1 ml/min.—0.2 ml of 50 % sodium acetrizoate (Triurol) was injected intra-arterially. Despite continued stimulation of the sympathetic chain, the blood flow then increased to 11 ml/min. In order to ascertain whether the effect of the sympathetic impulses ceased entirely

grafin), which have been considered to have fewer side effects.

It has been demonstrated earlier that intra-arterial injection of sodium acetrizoate (Triurol), even in small doses, produces considerable local vasodilatation in the peripheral arteries of the cat (Lindgren & Törnell, 1958). It was found that the blood flow could increase up to 10 times the initial value in 10–20 minutes. The vascular reaction was the same in all the tissues studied, i.e., skin, skeletal muscles and intestines. Dilatation of the cerebral vessels could also be demonstrated in carotid angiography with acetrizoate (Kågström, Lindgren & Törnell, 1958).

A report is given in the following of tests of sodium acetrizoate as a therapeutic medium in three human subjects. Animal experiments have also been performed. A study was made of the importance of the innervation for the reaction of the vessels of the peripheral muscles to sodium acetrizoate.

OBSERVATIONS ON HUMAN SUBJECTS

The vasodilator effect of sodium acetrizoate on the peripheral arteries was tested in three human subjects. In two cases it was a question of acute arteriospasm, presumably as a result of catheterization. On intra-arterial injection of acetrizoate, the spasm was relieved immediately, and did not recur. In the third case, an artery (ulnar artery) proved to be too narrow to allow catheterization. After injection of acetrizoate, the vessel dilated, so that the catheter could be introduced.

Case 1.—A 40-year-old man with a tumour of the stomach. Aortography of the coeliac vessels was performed. After premedication with morphine and scopolamine, a double-lumen catheter with balloon was introduced via the radial artery under local anesthesia (lidocaine without addition of a vasoconstrictor). The catheter advanced without difficulty to the superior part of the abdominal aorta, where the contrast medium was injected. The dose was 0.7 ml of 60 % Urografin (diatrizoate) per kg of body weight. The catheter was withdrawn, and the artery sutured with 4-0 Deknatel silk. Good pulsations were present distal to the site of suture.

Between 15 and 20 minutes after suture of the skin, the pulsations in the radial artery ceased. Papaverin (10 cg) was injected subcutaneously; two hours later, the radial pulse was still impalpable at the wrist. The hand was blanched, with incipient flaccid paralysis. The radial artery was exposed through the earlier incision, and the sutures in the vessel removed. No blood pulsated from the vessel. The incision was prolonged to 10–12 cm in length, so that the distal part of the brachial artery was exposed; it was found to be greatly contracted. On cautious passage of a ureteral catheter into the brachial artery, a small quantity of blood pulsated from the opening in the vessel for a short time, after which the pulsations again ceased. Blocking of the stellate ganglion had no effect. Local injection of 2 % procaine into the brachial artery via a catheter and periarterial application of procaine also failed to relieve the vasospasm.

After a further two hours, there were

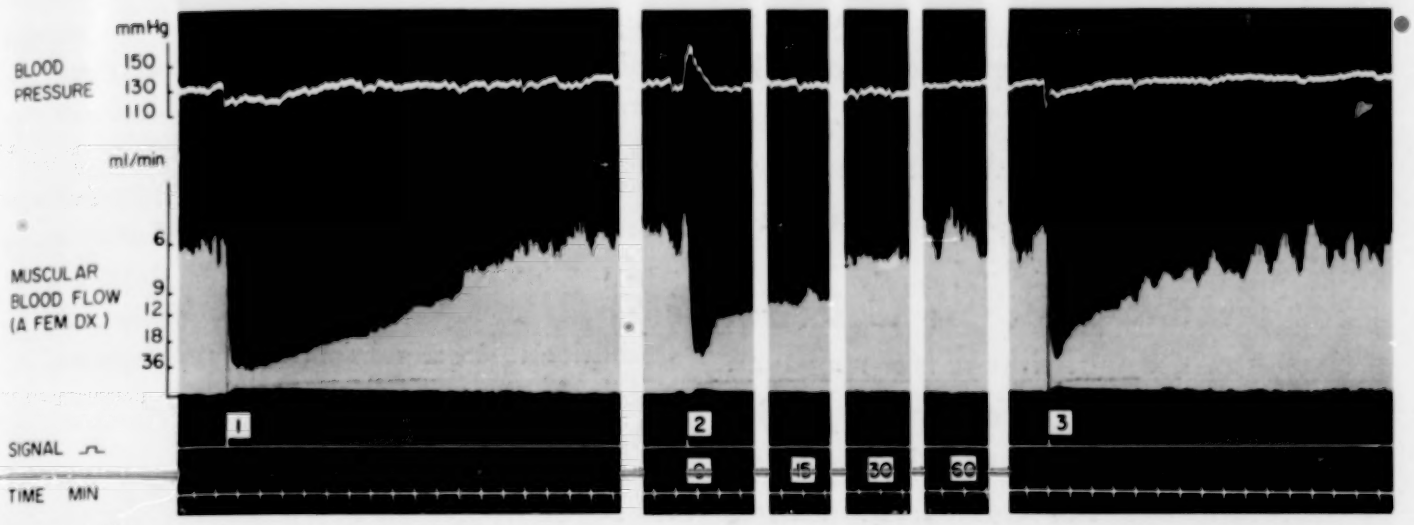


FIG. 2. Cat 3.8 kg. Dial anesthesia: 60 mg/kg body weight. Acetrizoate-induced vasodilatation before and after sympathectomy. *1*, Intra-arterial injection of sodium acetrizoate (0.2 ml, 50 %); *2*, abdominal sympathectomy—after momentary reduction of vascular tone, the flow gradually returned to the initial level; *3*, one hour later, repeated injection of 0.2 ml of sodium acetrizoate.

duced vasodilatation and an increase in flow. It can therefore be concluded that the acetrizoate effect is probably due to a direct action on the vascular muscles, and not on the sympathetic transmission. The tone is, however, evidently regained somewhat more rapidly after the acetrizoate effect in a vasomotorially denervated leg, but it is difficult to state whether this difference is dependent on its higher myogenic tone or on other factors.

DISCUSSION

The investigation presented here is not entirely comparable with those mentioned in the introduction, i.e., those of Demel & Sgalitzer and Klein. In the first place, we used a different contrast medium. Furthermore, no chronic circulatory insufficiency was present in our patients. The observations made in human subjects nevertheless indicate that sodium acetrizoate has a very marked vasodilator action on the arteries of the extremities, even in the presence of severe vasospasm.

We cannot state with certainty whether the arteriospasm was neurogenic or myogenic in our patients. In case 1, it is likely that it was a question of myogenic vasospasm, since blocking of the stellate ganglion was ineffective. Our earlier animal experiments (Lindgren & Törnell, 1958) lend support to the view that acetrizoate probably has a direct chemotoxic action on the vascular muscles. This is because vasodilatation appeared in both innervated and denervated vessels, and even when vascular tone was considerably raised by stimulation of the sympathetic trunk, for instance.

The experimental results thus indicate that acetrizoate has an effect on both myogenic and neurogenic vasospasm. It is, however, conceivable that the great increase in blood flow after acetrizoate that takes place in highly vascular tissues, such as the skeletal muscles, produces falling pressure in the peripheral arteries. This may be associated with a temporary impairment of circulation in less vascular structures, such as the skin, even though

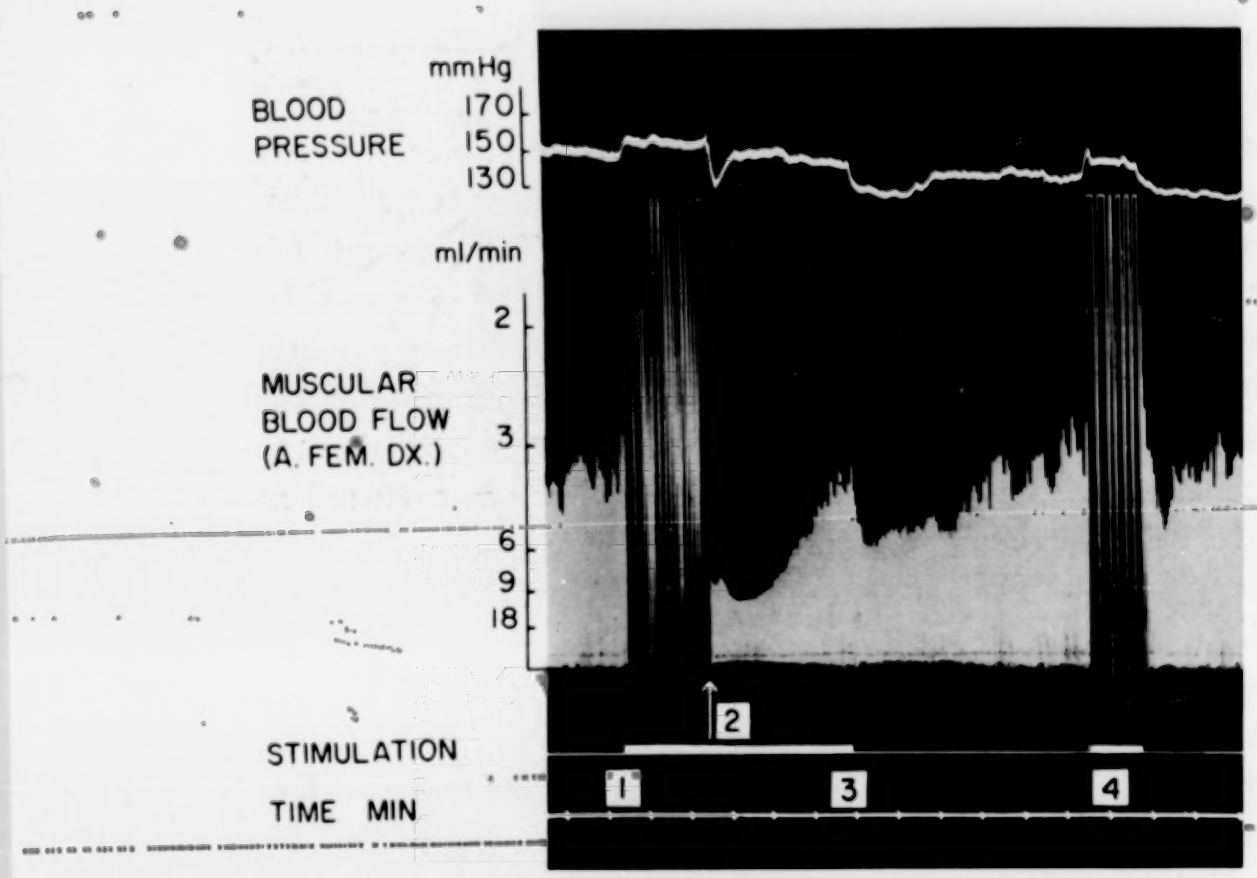


FIG. 1. Cat 1.7 kg. Dial anesthesia: 45 mg/kg body weight. Influence of sodium acetrizoate on the reduced muscular blood flow during sympathetic stimulation. *1*, Electric stimulation of abdominal sympathetic chain (10 impulses/sec., 1.5 V); *2*, intra-arterial injection of sodium acetrizoate (0.2 ml, 50 %); *3*, end of stimulation; *4*, stimulation repeated.

during dilatation with acetrizoate, the stimulation was interrupted at 3 in the figure. This resulted in a certain increase in blood flow, but not a marked one, indicating that the vascular paralysis had been fairly severe. Injection of acetrizoate did not, however, give rise to any lengthy vascular paralysis, since—when vascular tone had become normalized after 10 minutes—the normal response to stimulation of the sympathetic chain reappeared.

Vasoconstriction produced by exogenous administration of noradrenaline (intra-arterial injection) can also be inhibited by small doses of acetrizoate. Moreover, during acetrizoate-induced dilatation, the vessels are relatively insensitive to intra-arterially injected noradrenaline, even in fairly large doses (Lindgren & Törnell).

In order to study the importance of the vasomotor innervation for acetrizoate-induced vasodilatation, the following experiment was made (Fig. 2). The usual, practically maximal dilatation was produced by intra-arterial injection of 0.2 ml of 50 % sodium acetrizoate into the hind leg. The femoral blood flow increased rapidly from 6 ml to about 36 ml per minute. After 1–2 minutes the vascular tone gradually recovered and the blood flow reached its normal level within 15 minutes. The sympathetic chain, which had been exposed earlier in the experiment, was then excised on the right side, peripheral to L_3. A temporary increase in blood flow then occurred, as a result of vascular paralysis when the sympathetic vasoconstrictor impulses ceased. The vascular muscles, however, soon regained their tone, which was then myogenic. As can be inferred from Fig. 2, the blood flow had returned to the normal level after about one hour. A repeated injection of acetrizoate once more pro-

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Experimental Stereoangiography of the Coronary and Bronchial Arteries

BJÖRN NORDENSTRÖM, CARL-OLOF OVENFORS and GUNNAR WESTBERG

It has been demonstrated earlier by Fernström & Lindblom (1955), among others, that excellent stereoscopic pictures can be obtained of the abdominal aorta and its branches. One of the chief technical prerequisites has been the possibility of reducing the time interval between two exposures of the opacified vessels to a minimum. This has been achieved with rapid serial film changers now available. As far as the abdominal vessels are concerned, the conditions are relatively favourable. This is because positional changes in the vessels between exposures of the stereoangiograms are not necessarily particularly marked. The respiratory displacements of the abdominal vessels that may occur can be fairly easily avoided.

Considerably greater difficulties are associated with thoracic stereoangiography. Respiratory changes in position of the heart and vessels, as well as positional changes due to the cardiac pulsations, greatly hinder use of the stereoscopic technique for a study of the heart and thoracic vessels with injection of contrast medium.

The following experiment was made to test the possibility of obtaining stereoscopic angiograms of the coronary vessels. Two roentgen tubes were placed side by side, with an angle of 5° between the central rays. Owing to the size of the tube housings the focus-film distance with this angle was as large as 1.4 m. Each tube was fed by a separate 150 kV, 6-valve apparatus, which permitted intermittent exposure with each tube. A serial film changer (Elema type) was used, with a 30-cm wide roll film. The exposure time was 0.017 sec, with an interval of 0.040 sec between each pair of exposures.

A dog weighing about 10 kg was anesthetized with sodium pentobarbital injected intraperitoneally, and intubated. It was then placed, lying on its back, beside the vertical plane of the serial film changer. A catheter was introduced into the ascending aorta through the carotid artery. The contrast medium (1 ml of 76 per cent Urografin per kg of body weight) was injected through the catheter above the aortic valve, with simultaneous insufflation of oxygen through the bron-

vasodilatation appears here as well, as discussed earlier (Lindgren & Törnell). This could explain why Shaw (1956), for instance, observed a decrease in blood flow in the toes after femoral arteriography with acetrizoate.

For the therapeutic use of sodium acetrizoate, the fact that it is a roentgen contrast medium is presumably irrelevant. Investigations are now being made to ascertain whether the corresponding compound without the three iodine atoms, i.e., sodium 3-aminobenzoate, has similar vascular effects.

It has not been the intention in this paper to give any recommendations for the therapeutic use of sodium acetrizoate. We have only wished to point out that, in patients with acute spasm in the arteries of the extremities, sodium acetrizoate can be tried in addition to other spasmolytics. As far as the eventual use of acetrizoate in acute, severe vasospastic conditions is concerned, it is obviously important—as applies to other spasmolytic measures—to institute therapy at an early stage, before thrombotization of capillaries and arterioles has occurred. We also wish to stress the risk of brain damage associated with injection of sodium acetrizoate in large doses and high concentration into the brachial artery, should the substance flow in the retrograde direction, and pass into the vertebral and carotid arteries.

SUMMARY

Sodium acetrizoate has been observed to have a spasmolytic effect on the arteries of the extremities in three human subjects.

In the cat, marked vasodilatation has been found to result from intra-arterial injection of sodium acetrizoate. It is considered that this effect is due largely to a direct action of the contrast medium on the vascular muscles, and that it is independent of the innervation.

On the basis of observations in human subjects and in the cat, it is suggested that, in acute spasm of the arteries of the extremities, intra-arterial injection of sodium acetrizoate can be tried, in addition to customary spasmolytic measures.

ACKNOWLEDGEMENT

The expenses of this investigation were defrayed by a grant from Karolinska Institutet (Professor Erik Lysholm's foundation), which is gratefully acknowledged.

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From the Surgical Research Laboratory, Karolinska Institutet, Stockholm, Sweden

The Elimination Rate of Heparin from Plasma on Normothermic and Hypothermic Dogs

PER OLSSON, GÖRAN WILLIAM-OLSSON and HANS LAGERGREN

In order to decrease the demand of high perfusion minute volumes during extracorporeal circulation, ECC is sometimes combined with hypothermia (Senning, 1954; Crafoord & Senning, 1956; Young, Sealy, Brown, Hewitt, Callaway, Merritt, & Harris, 1956). ECC, however, calls for heparin as an anticoagulating medium. For a correct dosage of heparin and its antidote it is important to know if the elimination of heparin during hypothermia deviates from the conditions of normothermia.

In this work results are presented from experiments on the elimination of heparin from the plasma in normothermic and hypothermic dogs.

MATERIAL AND METHODS

The experiments have been carried out on ten mongrel dogs anesthetized with Nembutal Abbot 30 mg/kg bw intraperitoneally. Five adult animals and five puppies, whose age varied between five and seven months, were used. Heparin Vitrum, containing 100 IU/mg was given to different animals at the doses 2, 4 and 6 mg/kg bw.

The heparin elimination from plasma has been carried out for each dog in normothermia (35–37°C rectal temperature), and about 10 days later with the same quantity of heparin, at hypothermia (28–30°C) obtained by surface cooling in an ice water bath. Severe shivering, if any, was prevented by further Nembutal intravenously. Respiration was spontaneous in all experiments. The inferior vena cava was cannulated via a peripheral vein by a thin plastic catheter through which the heparin was injected and the blood sampled. After the heparin injection and the blood sampling, the catheter was carefully rinsed. The same method of sampling of blood and heparin determination was used as described in a previous paper published by Blombäck, Blombäck & Wallén (1955); Blombäck, Blombäck, Olsson, William-Olsson & Senning (1959).

The first sample was taken 5 minutes after the heparin injection and thereafter every 20 minutes during a period of 3 hrs. to 3 hrs. and 40 min.

RESULTS

The plasma heparin value determined 5 minutes after heparin injection was excluded. All of the values of heparin

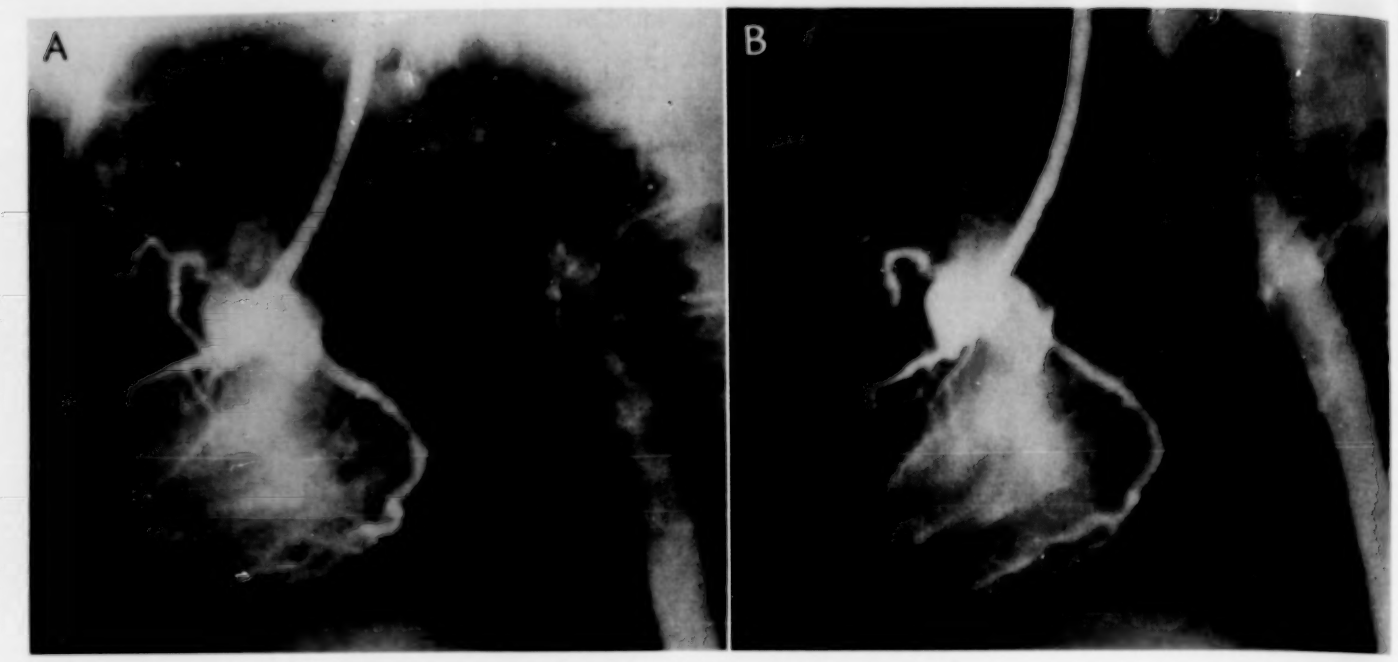


FIG. 1. Thoracic aortography in the dog. Stereoangiograms of the aorta, coronary vessels and bronchial arteries. Part of the contrast medium has regurgitated into the left ventricle.

chial tube to a pressure of about 25 cm of water. Application of constant intrabronchial pressure produced a brief period of apnoea with the thorax in the inspiratory position, and concurrent temporary arrest of the circulation through the aorta. This was done to facilitate passage of the contrast medium from the ascending aorta into the coronary vessels. Simultaneously with inflation of the lungs and injection of the contrast medium into the aorta, the stereoangiograms were exposed with a frequency of 3 exposures per second with each tube.

Fig. 1 shows a pair of stereoscopic pictures made in the experiment. The aorta with the coronary vessels, as well as the mediastinal and bronchial arteries, are filled with contrast medium. Despite the movements of the heart, the positional changes of the coronary vessels are so small that the stereoscopic effect is not markedly disturbed. The tortuous mediastinal and bronchial arteries appear more distinctly, and their course can easily be followed stereoscopically.

SUMMARY

It has been possible, in experimental stereoangiography in the dog, to obtain stereoscopic pictures of both the coronary arteries and aorta, as well as of the bronchial and mediastinal arteries. With sufficiently rapid changing of the two stereoprojections, the pulsations of the heart do not form any decisive impediment to obtaining stereoangiograms of these vessels. The respiratory positional changes in the heart and vessels can relatively easily be overcome if the examination is performed under anesthesia.

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TABLE.

Dosage of hep. mg/kg bw	Time in min. for 50 % decrease of plasma hep. concn. Normothermia	Hypothermia
	Adult dogs	
6	77	128
	77	148
4	81	100
	74	196
2	51	68
	Puppies	
6	52	110
	52	128
4	77	244
	38	85
2	48	80

DISCUSSION

The value of plasma heparin obtained 5 minutes after heparin injection varied considerably in relation to subsequent values and it is considered that this fact is caused by insufficient time for distribution of heparin in the blood volume and different organs. This phenomenon warrants further investigation and lies outside the scope of the present work, so we have excluded this value when dealing with the values for the heparin elimination.

The material is heterogeneous as to the animals' age and heparin dosage to establish the difference in disappearance of heparin during normothermia and hypothermia. Thus in all cases a slower elimination of heparin from the plasma is observed during hypothermia compared with normothermia.

Since hypothermia is generally considered to decrease the biological activities, the results of these experiments are to be expected. How the excretion and the metabolism of heparin proceeds under normal circumstances are not completely known. Copley & Schnedorf (1941) have, however, shown in dogs excretion of heparin in urine, and investigations by Monkhouse (1954) point to deterioration of heparin in the liver. With this information as a background it is of interest to compare the results in our experiments to the decrease in kidney function in hypothermia shown by Bergstrand & Sterky (1954) and to Brokaw's experiments on dogs (1949) which show a considerable decrease in bromsulphalein excretion at 30°C rectal temperature.

The diminished blood circulation and the lowering of O_2 consumption at hypothermia has been demonstrated by a number of authors as Bigelow, Lindsay, & Greenwood (1950), Hegnauer, Shriber & Haterius (1950), and Juvenelle, Lind & Wegelius (1952). Blood pressure and pulse rate are affected (Hegnauer *et al.*, 1950), and Penrod (1949) has shown that O_2 consumption to a large extent is influenced by various degrees of shivering and that the variations have their maximum at 27–30°C. In order to safeguard spontaneous respiration at hypothermia the anesthesia has in several of our experiments been superficial with slight shivering. Additional doses of Nembutal were only given to prevent severe shivering. The great scattering in the time of the fifty per cent elimination of plasma heparin at hypothermia—at the most 244 minutes and least 68 minutes—may therefore be partially explained by the effect of anesthesia variations on circulatory conditions.

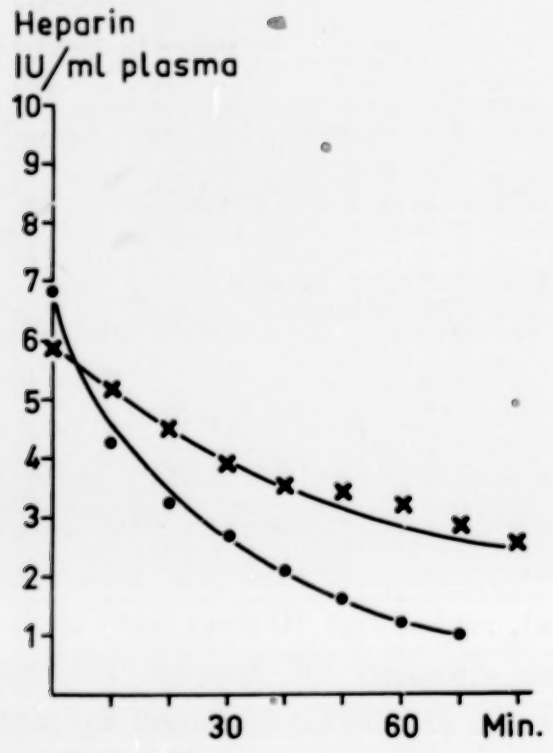


FIG. 1. The elimination of heparin in a puppy during normothermia and hypothermia. Dots indicate normothermia and crosses hypothermia.

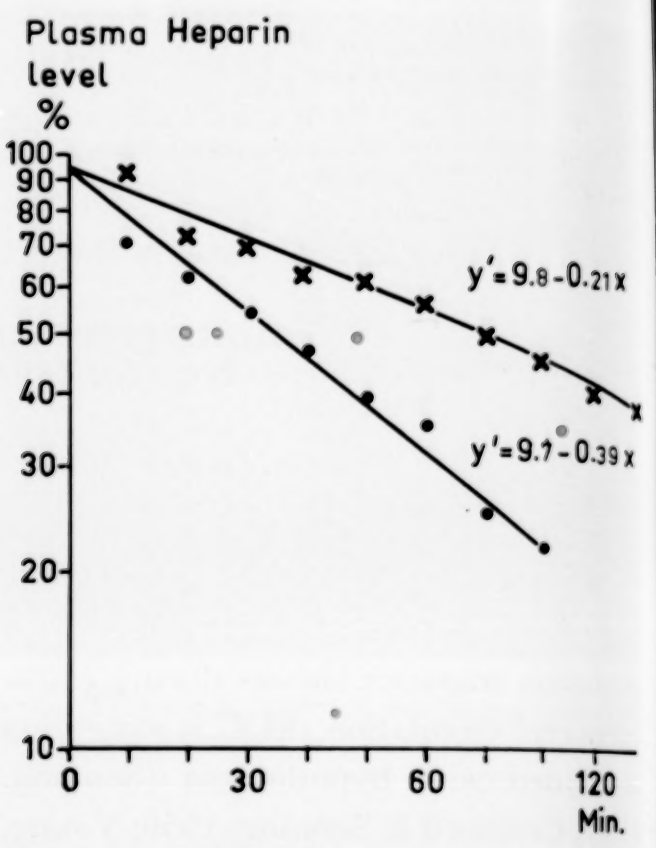


FIG. 2. The elimination of heparin in semilogarithmic scale in an adult dog. Dots indicate normothermia and crosses hypothermia. r^2 is 0.99 and 0.98 respectively.

concentrations in plasma from the rest of the samples varied between 9.1–0.26 IU/ml plasma.

The plasma heparin elimination curves for a puppy at normothermia and at hypothermia are shown in Fig. 1. In this case the first plasma heparin value—twenty-five minutes after heparin injection—lies lower at hypothermia than at normothermia, but in the total material the variations were large in this particular respect. The plasma heparin levels were not in direct proportion to the dosage of heparin in different dogs in either normothermia or hypothermia.

For each experiment the values of the heparin concentration were plotted in a semilogarithmic scale in per cent of the value obtained at 25 minutes. The plots were computed in regression, and the time for fifty per cent decrease of the plasma heparin concentration was obtained on the regression line. It appeared that the elimination curves both at normothermia and hypothermia were exponential, as illustrated in the case in Fig. 2. The condition is similar in all the experiments, and r^2 (the strength of regression), when calculated on nine to eleven values from each dog, varies in the total material between 0.95 and 1.00.

The fifty per cent decrease of the heparin concentration in the two groups was determined and the results appear in the table. The average time in the normothermic group is 63 minutes and in the hypothermic group 128 minutes. When the values are matched in pairs and the mean difference is calculated and tested for significance, $P < 0.001$ is obtained.

TABLE.

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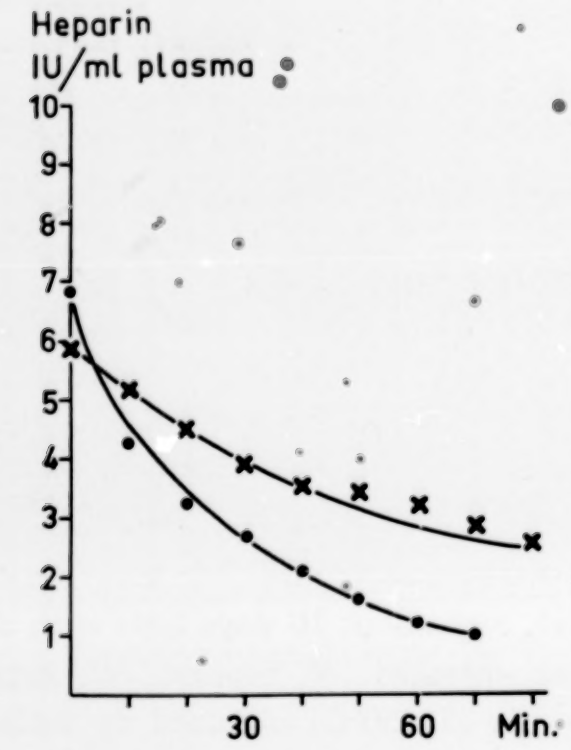


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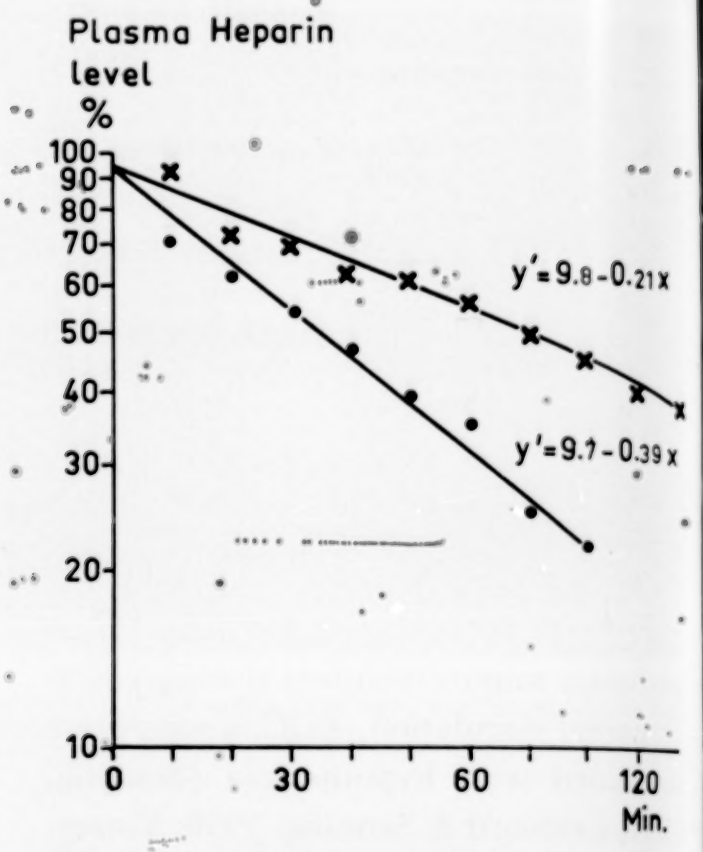


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Fatal Duodenal Hemorrhage in an Infant with Cardiac Malformation

GÖRAN WALLGREN and SALVADOR PALMA

Peptic ulcer and its complications, formerly thought to be an uncommon affliction during infancy and childhood, have been reported so frequently in the literature that this disease should now occupy an important place in the differential diagnosis of gastro-intestinal disorders in infants and children.

The incidence of the disease is difficult to assess, as we have no means of telling the number of undiagnosed cases in this age group. Holt (1913), Proctor (1925), Berglund (1929), Guthrie (1942) and Goldsberry (1951) have all, in an effort to obtain some information as to the frequency of the disease, studied large series of autopsies in children. From their figures it seems reasonable to assume the frequency of peptic ulcers in this age group to be in the range of 1–1.5 %, a vast majority of them being duodenal ulcers. These figures, however, do not represent the true overall frequency, as many of the reported ulcers are apt to be secondary to some other underlying disease in this material, and they should consequently be considered too high for the general population.

Another study to determine the frequency of the disease was carried out by Hutchins in 1944, who collected from the literature 243 cases of peptic ulcer in infancy, and by Alexander in 1955, who found in the literature reports of 50 cases of gastric ulcers in children.

The distribution of the disease in different age groups was studied by Karlström in 1949 in a material of 30 cases. He found the highest incidence in the age group 10–15 years. In 1953 Girdany reported an even distribution from 3 years of age and upwards in his material of 45 cases, and found no cases under 14 months of age. In 1941 Bird *et al.* also studied the distribution in 245 cases of duodenal ulcers in children reported in the literature, and found no fewer than 45 cases among infants less than 2 weeks old. The high incidence among the new-born can probably be explained by the fact that in this age group the ulcers are usually secondary to other diseases, and the diagnosis is in the vast majority of cases made on the autopsy table.

Bonnaire *et al.* (1916), Thelander (1939), Herbut (1943), Kellog (1951), Robertson (1954) and Abramson *et al.* (1957) have all reported ulcers in the

SUMMARY

The elimination of intravenously administered heparin from the plasma is followed in ten dogs both at normothermia and at hypothermia (28–30°C rectal temperature) through direct determination of plasma heparin. The elimination curve was exponential within the investigated ranges and the time for fifty per cent decrease of the heparin concentration was significantly longer at hypothermia than at normothermia—on an average 128 minutes compared to 63 minutes respectively.

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aorta and the pulmonary artery. The width of the aortic ostium was approximately 26 mm and that of the pulmonary artery 35 mm. The valves were all normally developed. The foramen ovale was closed and no other atrial septal defect was present. In the middle portion of the interventricular septum there was a defect in the muscular part of the septum measuring 12 mm in circumference. No other defects were present in the cardiovascular system. Distal to the pylorus there was a mucosal erosion about the size of a pea, and the microscopic examination revealed a duodenal ulcer that perforated the muscular wall and penetrated to the pancreas. The intestines distal to the ulcer were filled with tar-colored masses.

DISCUSSION

A *sine qua non* for the development of a peptic ulcer is the presence of a sufficient amount of gastric acidity. In 1942 Miller studied the gastric juice in prematures and normal new-born infants and followed the changes in acidity during the first years of life. He concluded that in normal infants there is during the first days of life a high acidity in the ventricle which gradually decreases, and is not regained until around three years of age, while in prematures a complete achlorhydria is a common finding. The prerequisite of an acid gastric content is thus present in most new-born infants. The development of a peptic ulcer, however, also depends upon the presence of a *locus minoris resistentiae* in the gastro-intestinal mucosa itself. This mucosal defect in the new-born is usually produced by associated diseases or malformations.

Herbut (1943) and Sarinang (1956) reported cases of peptic ulcers in infants, where congenital malformations in the G.I. tract were supposed to be the etiological factor. Others (Gerdine *et al.*, 1915; Kempton *et al.*, 1953) have suggested infections as the main provocation for the ulcer; and traumatizing conditions such as burns have also been reported as initiating factors (Curling, 1842). It is generally agreed that the more cachectic infants are, the more liable are they to develop gastro-intestinal ulcers (Karlström, 1949; Bernheim *et al.*, 1954). Since Cushing in 1932 pointed out the relationship between the mid-brain and gastro-intestinal ulceration, which is due, he suggested, to changes in the vasomotor system in the brain, other authors have reported this encephalo-intestinal interaction also in children (Opper *et al.*, 1938; Schlumberger, 1951).

It is evident that there is a rich variety of etiological factors responsible for the production of peptic ulcers in infants, quite apart from the wide field of cases of psychosomatic genesis occurring in the adult.

It seems plausible that the circulatory changes, as well as the influence upon the physical properties and oxygenation of the blood in infants with cyanotic heart disease, might constitute the necessary conditions for the initiation of a mucosal damage. In 1950 Friesen, in an attempt to explain the genesis of the "Curling ulcer", demonstrated experimentally that hemoconcentration alone is capable of initiating the production of

newly born with fatal complications, such as perforation or hemorrhage. In 1923 Lee *et al.* reported a case with ulceration and perforation already in utero. Beattie *et al.* in 1952 and Montcrief in 1954 published cases of complicated ulcers in very young infants, where perforation and gastro-intestinal hemorrhage were successfully treated with surgery.

The peptic ulcer in the new-born infant, through its lack of tendency to scarring and the high incidence of gastro-intestinal hemorrhage connected with it, is in itself very often a fatal disease, and might well be termed "acute malignant ulcer".

The present report deals with a fatal gastro-intestinal hemorrhage in an infant with a complex cardiac malformation, which is to our knowledge the first such association reported in the literature.

CASE REPORT

A six weeks old girl weighing 2510 g at birth was admitted to the hospital on account of suspected cardiac malformation. She was the product of a normal gestation and an uneventful delivery. She had failed to thrive and had had attacks of cyanosis, particularly at feeding time. On admission she was somewhat undernourished, with a body weight of 2790 g, and had a pale cyanotic color. She had marked shortness of breath and signs of right ventricular insufficiency. The liver was palpable 4–5 cm below the costal margin. There were no signs of peripheral edema. There was a slight systolic thrill over the apex, where a systolic murmur of fifth degree intensity was also heard. The second heart sound over the base was single and accentuated. Peripheral pulses were normal. The electrocardiographic tracings showed signs of atrial enlargement and combined ventricular hypertrophy. Heart rate 150/min. Roentgenological examination of the chest showed a generally enlarged heart with increased vessel markings in the pulmonary fields, indicating left-to-right shunt. The relatively marked narrowness of the outflow-tract suggested transposition of the great vessels. The child was treated with digitalis, diuretics and oxygen, and there was a temporary improvement. The general state of the child was, however, very labile, with frequent periods of pronounced cyanosis and respiratory distress. In spite of treatment, the general condition of the child deteriorated and signs of marked pulmonary stasis were noticed. The roentgen examination showed an increasing heart size. In order to decrease the child's demand for oxygen, the rectal body temperature was reduced to 34°C by administration of cooled oxygen to the incubator. This latter therapeutic measure improved the general state of the child temporarily, but on the 30th day of life, after having had tarry and sticky stools for two days, the child expired in a state of marked cardiopulmonary insufficiency. The post-mortem examination revealed pulmonary stasis with basal edema and minor hemorrhagic areas in both lungs. The heart weighed 68 g and had a marked enlargement of all four cavities. The thickness of the left ventricle wall was 10 mm and that of the right 8–9 mm. There was complete transposition of the

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a gastro-intestinal ulcer. It is well known that hemoconcentration occurs also in cyanotic heart lesions, and this phenomenon may thus be considered a potential etiologic factor. Also the production of visceral venous stasis, as well as long-lasting tissue hypoxemia, may conceivably render the intestinal wall extremely vulnerable. The ischemic status of the brain may also have played a major role (Cushing, 1932), although no other signs of cerebral dysfunction were present in this case.

The increased antithrombin activity present in cyanosed patients described by De Sario in 1957 is well worth mentioning in an explanation of the intense gastro-intestinal hemorrhage that developed in the case reported.

SUMMARY

A report is given of a case of congenital heart disease and bleeding peptic ulcer coexisting in the neonatal period. To our knowledge this is the first such report in the literature. The relevant literature is reviewed and several explanations are presented to indicate more than casual relationship between the two phenomena.

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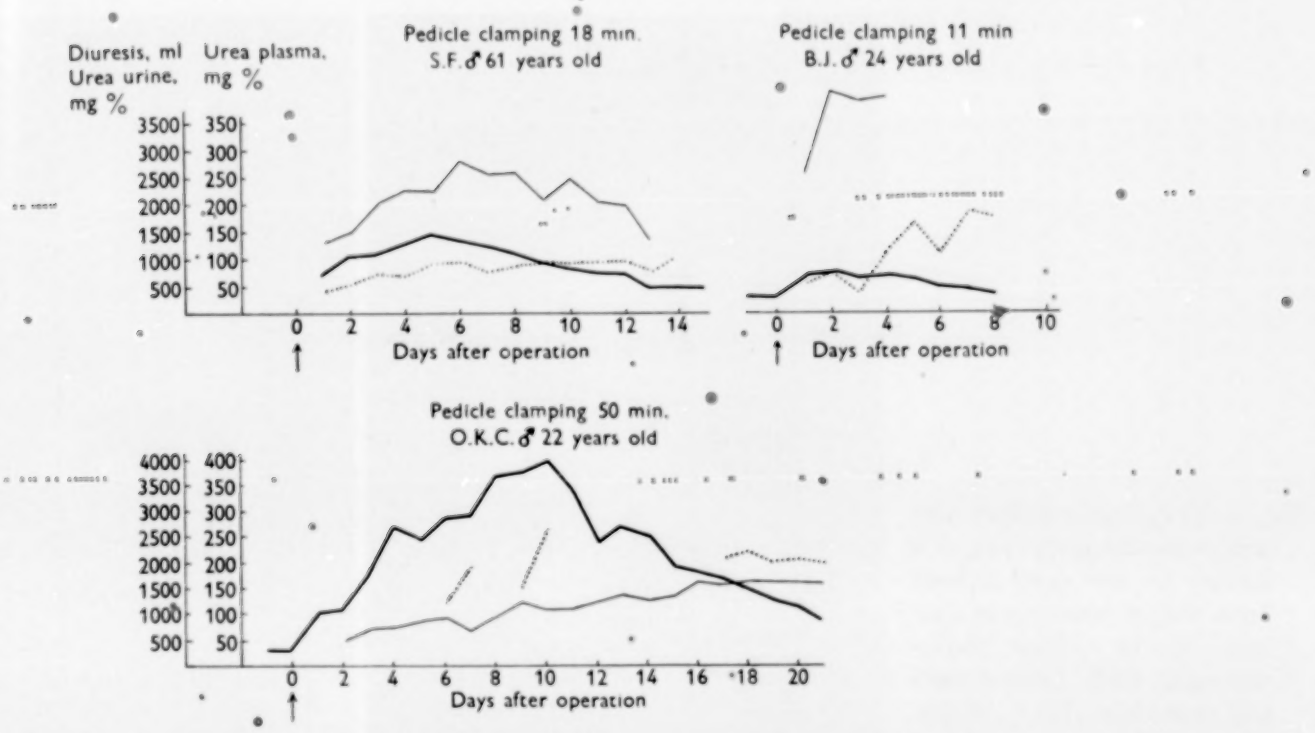


FIG. 1. The postoperative reaction to partial renal resection following clamping of the pedicle for 18 min., 11 min., and 50 min. ..... = diuresis; —— = urea urine; —— = plasma.

dogs after 2–3 hours of clamping. After clamping for 1 hour two of four dogs died.

Ischaemia at 5–17°C in the kidney did not provoke fatal uraemia until after 8 hours of clamping (A + V) and after 12 hours of clamping (A).

Thus with local cooling of the kidney to 5–17°C the tolerance in respect to ischaemia increased about fivefold or more.

Studies of the renal function following ischaemia showed that local cooling did not change the type of functional depression but protected the renal parenchyma so effectively that the renal function was entirely restored after 2–4 weeks.

CLINICAL EXPERIENCE

Studies of the renal function after partial resection of the kidney (Semb, 1953) have shown that there are especially two operative factors which may injure the renal function:

(*a*) Direct local trauma caused by manual pressure on and pulling of the kidney during operation. This factor can be appreciably reduced by employing an appropriate incision which allows a more delicate dissection of the kidney.

(*b*) Ischaemia, by clamping of the vessels or manual compression of the renal tissue in order to operate in a blood-deficient field, causes a post-operative reaction which depends upon the duration of the ischaemia. After 10 minutes of clamping there is a moderate reaction, after about 20 minutes a distinct and fairly serious reaction, and after 50 minutes a dangerous uraemia (Fig. 1).

Local cooling of the kidney in order to reduce the postoperative reaction may be desirable in operations on kidneys which have a considerably diminished total function and therefore small reserves. I have tried this on four cases of bilateral coral calculus with excellent results.

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Local Cooling of the Kidney for Protection against Operative Trauma

CARL SEMB

It has been found that *general* cooling, as used in brain and heart surgery, lowers the metabolism, and hence the oxygen requirement, of the tissue. General hypothermia nevertheless has its limitations and complications, which reduce its clinical uses. The temperature can scarcely be brought below 26–28°C, and with falling temperature the risk of complications increases.

Local cooling of individual organs as protection against operative trauma has been little employed in surgery. With this method it is possible to lower the temperature of the organ to considerably less than 26–28°C while maintaining the general temperature of the body or reducing it only to a minimal extent. In this way a more effective cooling is attained and general complications are avoided.

At the University Institute of Experimental Medical Research and at Department III, Ullevål Hospital, Oslo, local hypothermia of kidney and brain has been employed for the past three years experimentally and clinically.

EXPERIMENTAL EXPERIENCE

Experiments earlier Reported by Birkeland, Vogt, Krog & Semb (1959) were made on 24 dogs to examine the effect of local cooling down to 5–17°C of a single remaining kidney which was at the same time subjected to ischaemia by shutting off the blood supply for 1–12 hours.

The cooling was done with a double plastic bag filled with sterile ice and placed round the exposed kidney.

Ischaemia was effected by clamping of renal artery alone (A) or of the renal artery and renal vein (A + V).

The temperature was continuously measured in the kidney tissue and in the rectum throughout the experiment.

The reaction of the renal function after clamping was followed by tests of clearance for urea, inulin, P.A.H. and Tm. P.A.H.

These studies (28 experiments on 24 dogs) produced the following results:—

Ischaemia at 37°C in the kidney (A and A + V) provoked fatal uraemia in all

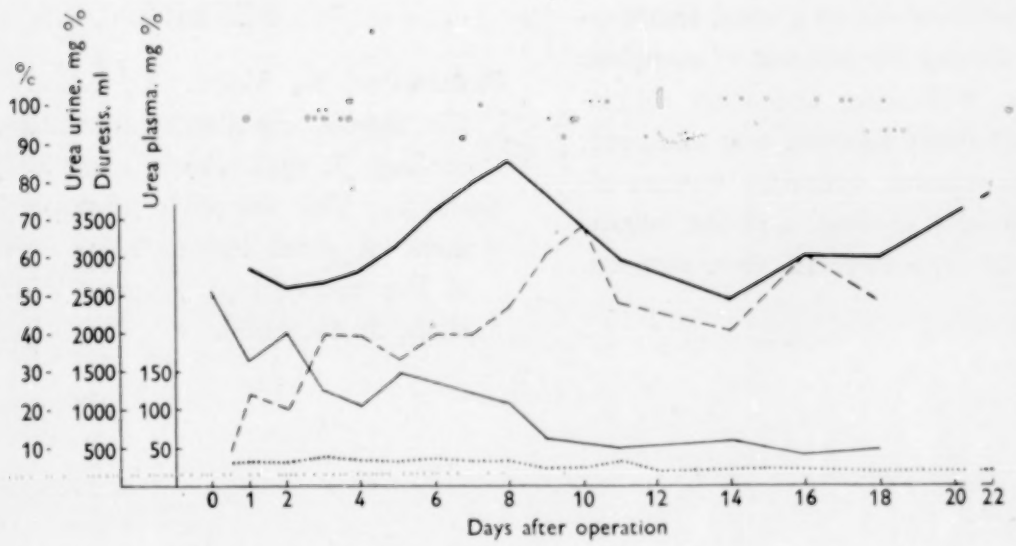


FIG. 4. Functional tests before and after partial resection of the single remaining kidney under hypothermia, showing minimal reaction. G. W. L. Clamping time, 26 min. Temperature of the kidney at the start of resection, 23.4°C. ——= urea clearance; —— = urea urine; – – – = diuresis; ..... = urea plasma.

in the center group of calyces which had resisted prolonged treatment with antibiotics over a period of 18 months. A local resection was made of the central field with the entire pedicle (A + V) clamped for 26 minutes. The kidney was cooled down to 23°C during the operation. The resection proceeded without special complication, and subsequent urography revealed the excellent result obtained (Figs. 2 and 3). Tests of renal function before and after operation showed insignificant lesions with barely measurable diminution of function (Fig. 4). The urine was strongly concentrated from 24 hours onwards following the operation. Urea in plasma showed no measurable changes in the post-operative period. Urea clearance fluctuated between 60 and 80 % of normal, as it did before the operation. Comparing this reaction after operation under hypothermia with the reaction which usually follows an operation without hypothermia, the difference is striking. Follow-up three years later showed unchanged function.

These experiences show that local cooling can provide a high degree of protection for the renal parenchyma against operative trauma.

SUMMARY

A method developed for local cooling of the kidney without lowering of general body temperature was used experimentally and clinically.

Experimentally (total 24 dogs), at a kidney temperature of 5–17°C complete renal ischemia was tolerated for 7–12 hours as compared to 1 hour at 37°C.

Clinically, at ordinary body temperature, it was shown that clamping of the renal pedicle for 10, 20 and 50 minutes during resection resulted in moderate, fairly serious and dangerous impairment of renal function respectively.

Employing local cooling during operation for bilateral coral calculi in four patients yielded excellent results.

Detailed data were presented from one patient subjected to partial resection of the one remai-

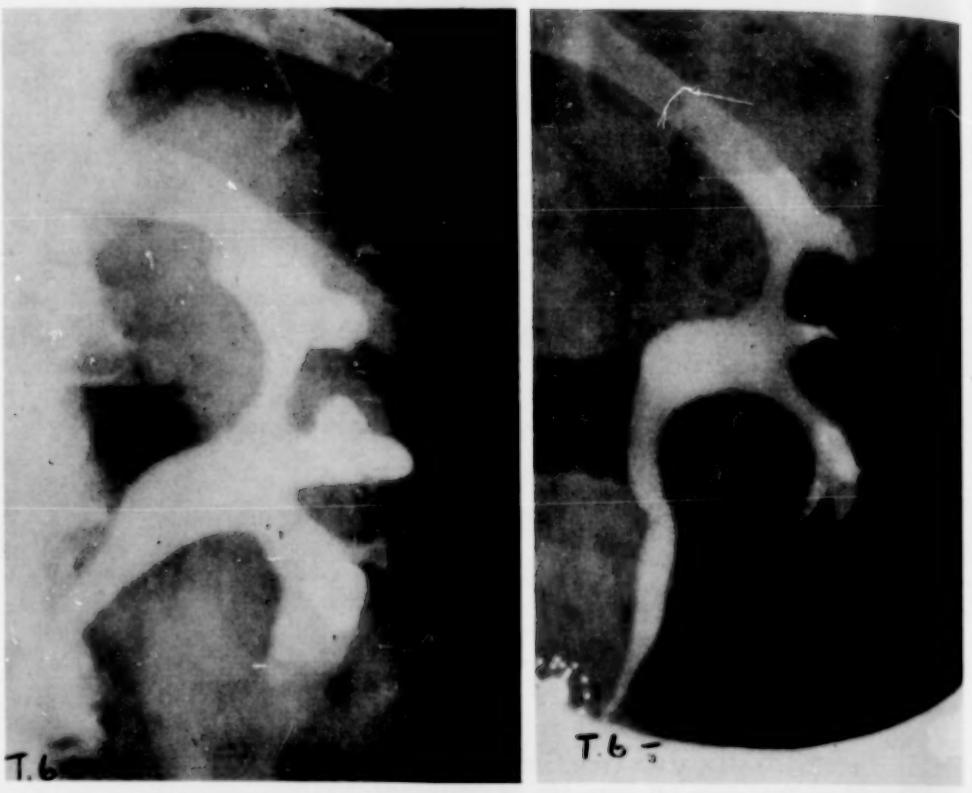


FIG. 2. Urography before and after partial resection of a cavity in the central field in a single remaining kidney under local hypothermia. *Left*, before partial resection, Tb +. *Right*, after partial resection, Tb –.

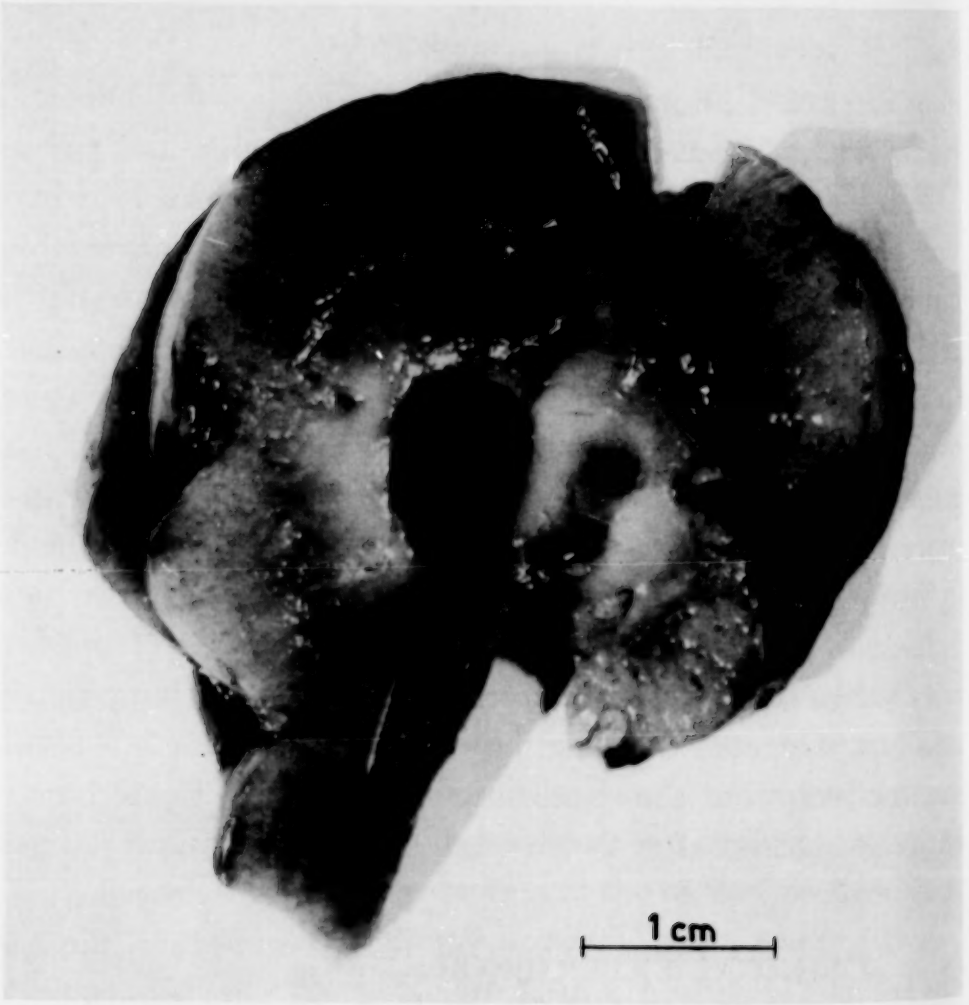


FIG. 3. Section of kidney with tubercular cavity in center.

The need is greatest in operation of a single remaining kidney, especially when clamping of the renal pedicle is required for 15–20 minutes in order to be able to perform satisfactory surgery.

A typical case of this kind was a 28-year-old man whose right kidney had been removed many years previously owing to tuberculosis. In the remaining left kidney there was a tubercular cavity

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ning kidney for tuberculosis at a renal temperature of 23.4°C during 26 minutes of complete pedicle clamping. Following operation no obvious reduction of renal function was observed.

The protection against operative trauma afforded by local kidney cooling, and the advantages over general hypothermia, were stressed.

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